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TOTAL SYNTHESIS OF 5-EPIKESSANE, DEHYDROKESSANE AND Δ^5-DEHYDROKESSANE

by

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A THESIS
SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH
IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE
OF DOCTOR OF PHILOSOPHY

DEPARTMENT OF CHEMISTRY

EDMONTON, ALBERTA
FALL, 1977

THE UNIVERSITY OF ALBERTA

FACULTY OF GRADUATE STUDIES AND RESEARCH

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research, for acceptance, a thesis entitled

TOTAL SYNTHESIS OF 5-EPIKESSANE, DEHYDROKESSANE
AND Δ^5-DEHYDROKESSANE

submitted by SING PING LEE in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

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Supervisor

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Josef Takats

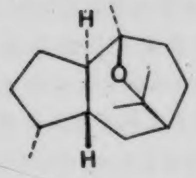
Date: Sept. 15, 1977

ABSTRACT

A stereoselective total synthesis of a hitherto unreported epimer of the naturally occurring sesquiterpene kessane (I), namely, 5-epikessane (II), and two unsaturated derivatives, dehydrokessane (III) and Δ^5-dehydrokessane (IV) has been achieved. In developing the synthesis a new approach for constructing the hydroazulene system was introduced. Primarily, the method involves the construction of a suitable tricyclo[5.3.0.0^{2,6}]decane system by photochemical means followed by specific cleavage of a carbon-carbon bond of the resulting cyclobutane ring.

Photocycloaddition of 1-acetoxy-2-carbomethoxycyclopentene and 4-acetoxy-2-cyclopentenone followed by acid treatment of the resulting photoadducts gave enone V. Treatment of V with a complex prepared from methylmagnesium bromide and cuprous iodide followed by thioketalization of the resulting ketone VI gave the thioketal VII. Reduction of VII with Raney nickel afforded the ester VIII which on reduction with lithium aluminum hydride gave rise to diol IX. The 1,3-glycol cleavage of IX with *p*-toluenesulfonyl chloride in pyridine furnished keto olefin X which was subsequently converted to β-keto ester XI using sodium hydride and dimethyl carbonate. Treatment of XI with sodium hydride and methyllithium gave rise to ketol XII. Oxymercuration-

reduction of XII effected the ether ring formation to give the keto ether XIII. Reduction of XIII with lithium aluminum hydride followed by dehydration of the alcohol XIV then gave the dehydrokessane (III) and Δ^5-dehydrokessane (IV). Reduction of XV, obtained by phosphorylation (N,N-dimethylphosphoramidic dichloride and dimethylamine) of XIV, with lithium in ethylamine completed the synthesis of 5-epikessane (II). Alternatively keto ester XI was converted to enol ether XVI using sodium hydride and chloromethyl methyl ether. Lithium-ethylamine reduction of XVI followed by treatment of the product with methyllithium afforded alcohol XVII. Oxymercuration-reduction of XVII also gave 5-epikessane (II).



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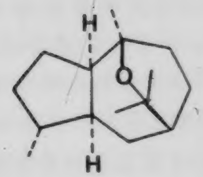

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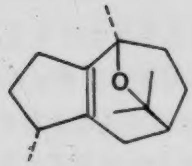

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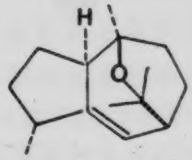

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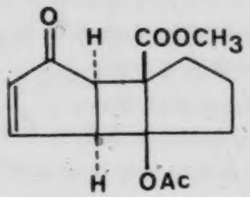

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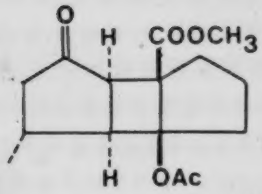

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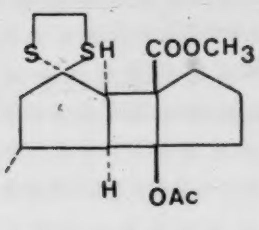

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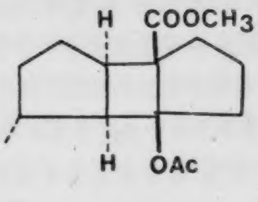

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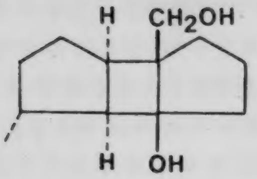

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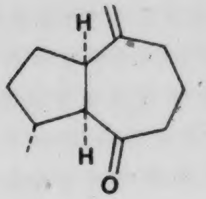

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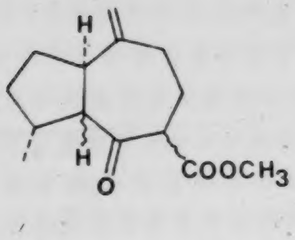

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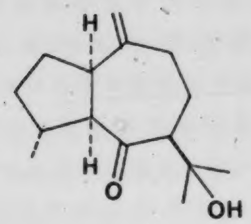

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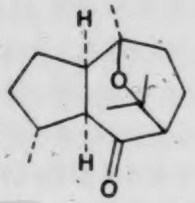

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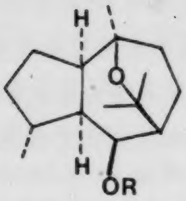
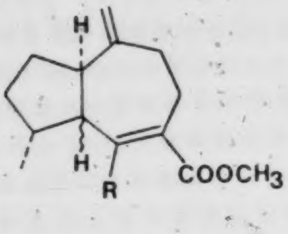
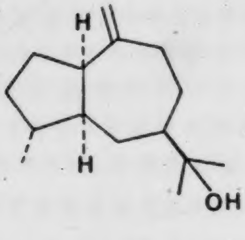


XIV: $R = H$

XV: $R = PO[N(CH_3)_2]_2$



XVI: $R = OCH_2OCH_3$



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INTRODUCTION

It had long been recognized that certain essential oils, when subjected to mild acid treatment, oxidation or distillation, developed a blue color. These blue substances, collectively known as azulene[1] had mystified and intrigued chemists for nearly three quarters of a century until 1936 when Pfau and Plattner (2) formulated the structure 1 for the parent azulene. The structural assignment was confirmed by a total synthesis and since then a number of substituted azulenes have been prepared (2).

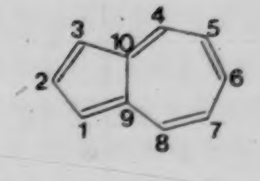
Sesquiterpenes based on the hydroazulene (hydrogenated version of 1) skeleton are widely distributed in nature. The early development of their structural chemistry was facilitated by the research into azulene 1 and its derivatives. More specifically, by a dehydrogenation process, naturally occurring compounds often gave rise to simple substituted azulenes of known structures whereby the carbon skeleton of the parent molecule could be established without much difficulty (3). For example, the gross structure of guaiol 2 was identified by its dehydrogenation with sulfur to the known compound S-guaiazulene 3 (4). Although convenient, the dehydrogenation method was not entirely reliable since it was frequently accompanied by the skeleton rearrangement. It was thus not unusual that, misled by the available information, the investigators arrived at errous conclusion of the carbon skeleton of the parent compound. β-Vetivone, for instance, had for many years been considered to possess structure 4 mainly due to its dehydrogenation to give vetivazulene 5 (5), and it was not until recently that an unambiguous synthesis revealed its correct constitution as 6 (6,7,8).

---

[1] The name azulene was initially applied in 1863 by Piesse (1) to the blue substance which he obtained from the essential oil of wormwood. It had since been retained for the parent hydrocarbon 1.

In recent years, the development of natural products chemistry has been greatly accelerated by the refined isolation and purification techniques, as well as by the availability of the far more sophisticated analytical methods. The field of hydroazulenic sesquiterpenes makes no exception and during the last two decades or so, a vast number of the naturally ocurring compounds of this class have been isolated and, in spite of their structural complexity, many have been fully characterized (9,10,11).

With few exceptions [e.g. Mexicanin E (7) (12) a fourteen carbon molecule], three carbon substituents in the form of two one-carbon units and an isopropyl group are commonly observed in hydroazulenic sesquiter-



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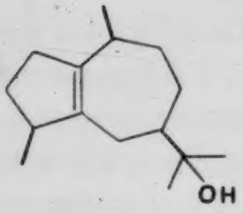

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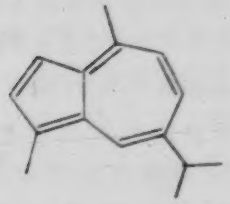

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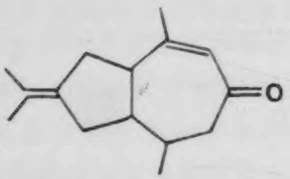

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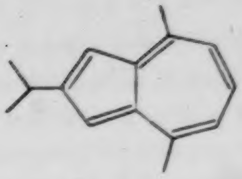

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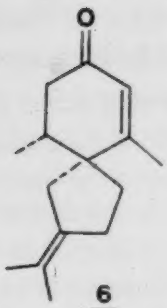

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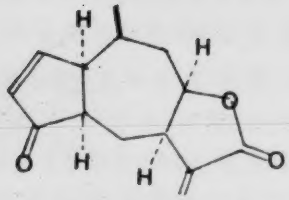
penes. Differing from each other in the substitution pattern, four families of this class of natural products are known. The major one is the guaianolide family of which guaiol 2 is a representative member. As also observed for pseudoguaianolide and daucane-type sesquiterpenes (*vide infra*), additional carbocycle [e.g. aromadendrene (8) (13)] or oxygen-containing rings in form of an ether linkage [e.g. kessane (9) (14)] or a lactone linkage [e.g. jacquinelin (10) (15)] or both [e.g. arboresin (11) (16)] are often present in guaianolides. From a biogenetic point of view, guaianolides are considered to be normal products in which the linkage of three isoprene units follows strictly the head-to-tail rule (17,18).

Pseudoguaianolides and zierone 12 differ from guaianolides in the location of a methyl unit and the isopropyl group respectively as a result of the migration of such groups during the biosynthesis (18,19). Zierone (12) (19,20,21,22) is the only member of the so-called zierazulene (13) family[2]. Sesquiterpenes of

---

[2] Prior to its correct structural assignment, zierone (12) was believed to have the same skeleton as that of zierazulene (13), since its dehydrogenation resulted in exclusion formation of the latter compounds. Natural products possessing the zierazulene skeleton, at present, still remain unknown.



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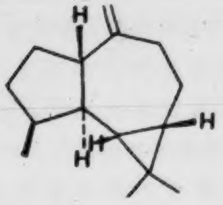

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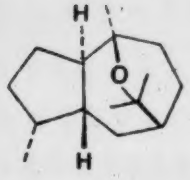

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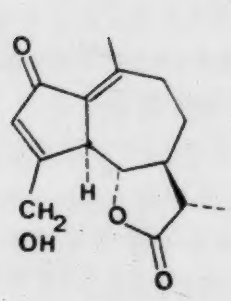

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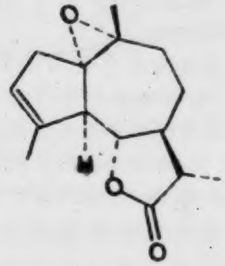

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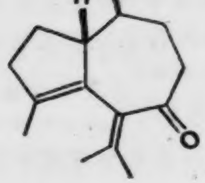

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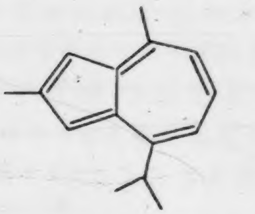
the pseudoguaianolide family are also large in number. Confertin (14) (23) and ambrosin (15) (13) are two representative examples.

Several natural products such as daucol (16) (24) and carotol (17) (25) are known to possess the daucane (18) skeleton which represents the fourth variation of hydroazulenic sesquiterpenes in carbon substitution pattern. It is noted that arrangement of the three isoprene units in daucane (18) also follows the normal head-to-tail manner and that its biosynthesis from farnesyl pyrophosphate proceeds by a mode of cyclization (26) fundamentally different from that of the other types of hydroazulenic sesquiterpenes mentioned earlier.

Although the physiological function of hydroazulenic sesquiterpenes in plants remain to be understood, some have been shown to be highly odoriferous compounds (27) and some found to have potential medicinal use (28,29,30). These interesting properties coupled with the chemical challenge presented by these rather complex molecules have stimulated considerable efforts in recent years in the search for new efficient methods for the construction of suitably functionalized hydroazulenes (31). The developed methods, some of which have been successfully applied to the syntheses of natural products and/or structurally related compounds,



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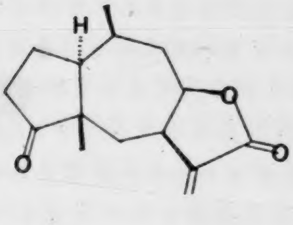

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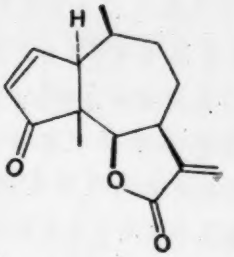

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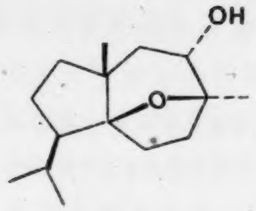

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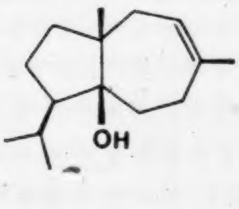

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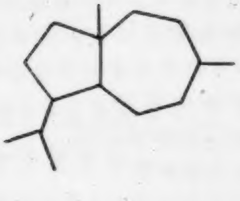

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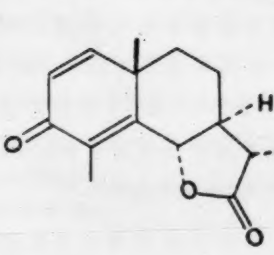
can be classified in three major approaches as follow.

(i) Modification of bicyclic system containing cyclohexane rings.

Bicyclo[4.4.0]decane and bicyclo[4.3.1]decane derivatives can theoretically be rearranged to hydroazulenes involving 1,2-migration of a specific carbon-carbon bond. This principle has been recognized and several methods developed accordingly. Although quite lengthy, by virtue of the better understanding of the cyclohexane system and the relative conformational rigidity of such a system, these methods often permit good control of the stereochemistry of the precursors and consequently that of the rearranged products. A classical example for the transformation of the decalin system to hydroazulene skeleton is the photochemically induced rearrangement of santonin (19) to isophotosantonin (20) (32). Using this method, Piers and Cheng converted the known dienone 21 to ketol 22, which on further modification afforded α-bulnesene (23) (33,34). Other successful syntheses of hydroazulenic sesquiterpenes through the photochemical rearrangement of decalins include those of dihydroarbiglovin (24) (35), achillin (25a) (36), deacetoxymatricarin (25b) (37) and arboresin (11) (38). Caine and Ingwatson reported the synthesis of (-)-cyclocolorene (26) from (-)-maalione (27) involving photoly-



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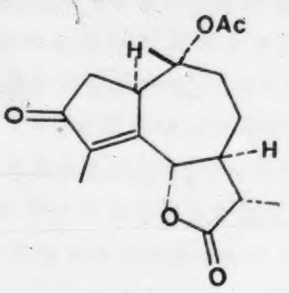

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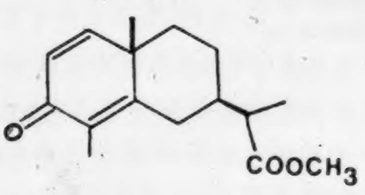

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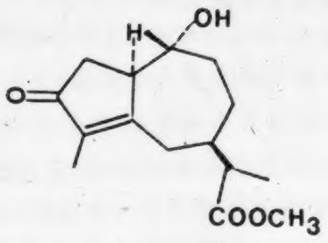

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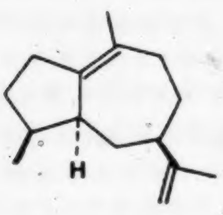

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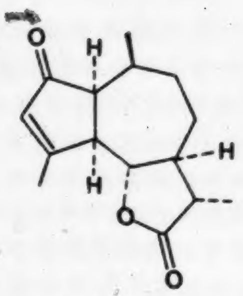

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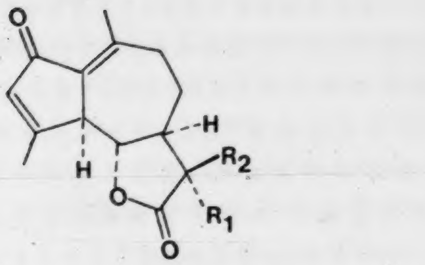
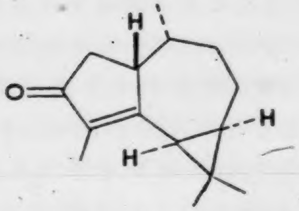


25a : $R_1 = H$; $R_2 = CH_3$

25b : $R_2 = CH_3$; $R_1 = H$



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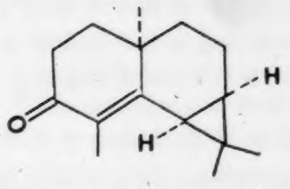

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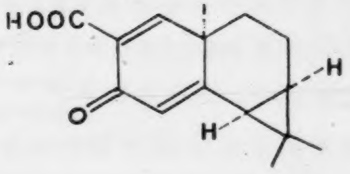

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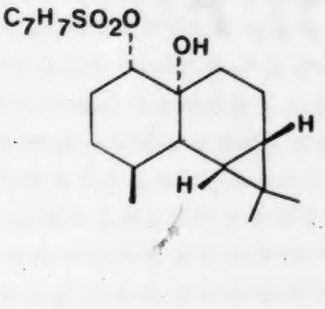

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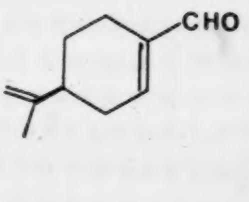

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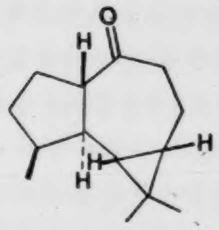

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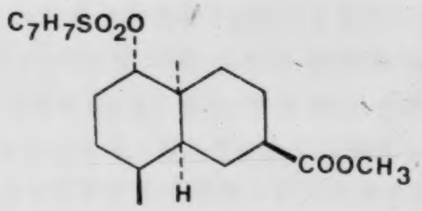

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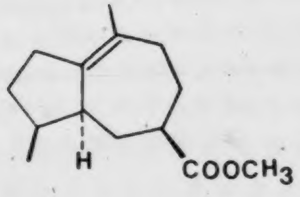

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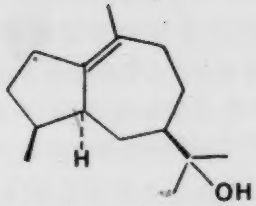

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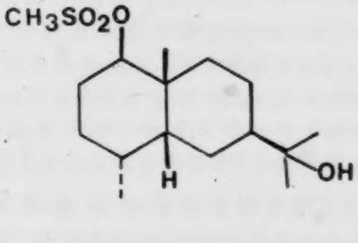

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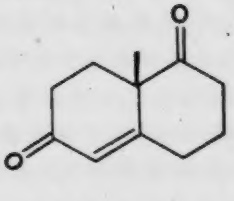
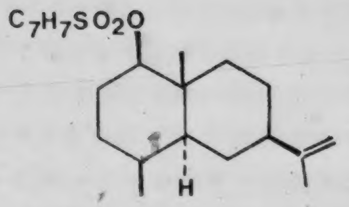


36

sis of dienone 28 as a key step (39).

Solvolytic rearrangement of suitably substituted decalins to hydroazulene derivatives has also ample examples. The feasibility of such a process was first demonstrated by Büchi and his co-workers in their elegant synthesis of (-)-aromadendrene (antipode of 8) in which the crucial step was the solvolysis of tosylate 29 prepared from (-)-perillaldehyde (30) to apoaromadendrene (31) (40). More recently, Kato, *et al*., (41) reported that tosylate 32 on solvolysis gave rise to 33, a known intermediate for bulnesol (34) synthesis. This procedure was further extended by the same group of investigators to the total synthesis of kessane (9) (42) in which solvolysis of the *cis*-fused decalin derivative 35, prepared from the well known Wieland-Miescher ketone 36 (43), induced both the desired skeletal rearrangement and the ether ring closure to give 9 in 30% yield. A similar route was also used in a recent synthesis of bulnesol (34) and α-bulnesene (23), involving the transformation of Wieland-Miescher ketone 36 to tosylates 37 and 38 and the solvolysis of the latter compounds to give the target molecules (44).

Solvolysis of functionalized bicyclo[4.3.1]decane derivative as a means for the construction of hydroazulene system has been extensively studied by Marshall and Partridge (45) and highlighted in a total synthesis



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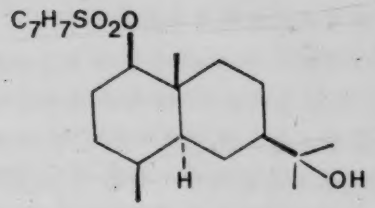

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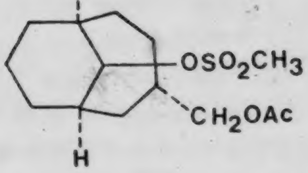

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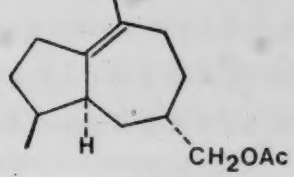

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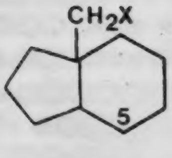

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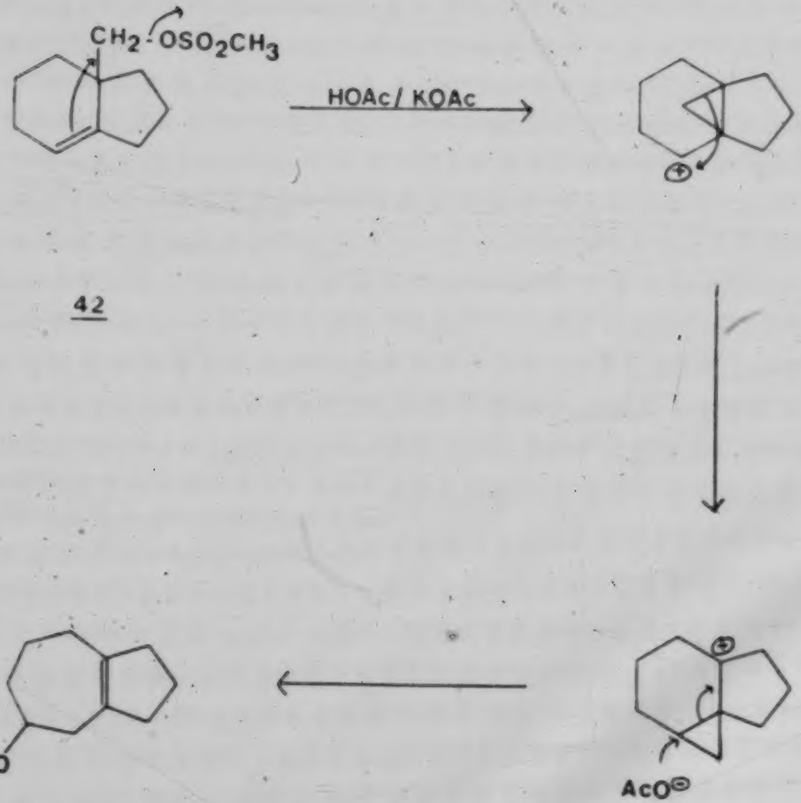
of bulnesol (34) involving, as a key step, the solvolytic rearrangement of mesylate 39 to olefin 40.

One carbon ring expansion of hydroindane system has also found use in the preparation of functionalized hydroazulenes. Solvolysis of saturated hydroindanes of general formula 41 (x = leaving group) gave rise, as expected, to all three possible Wagner-Meerwein rearrangement products (with respect to carbon skeleton) without much selectivity (46). The presence of a C-5 double bond, however, has been shown to alter markedly the course of reaction giving predominantly the hydroazulenic product. For instance, acetolysis of 42 resulted in the preferential formation of hydroazulene 43 (47). A mechanistic rationale (scheme I) has been postulated to account for these interesting findings. The transformation of mesylate 44 to 45 by acetolysis in connection with a total synthesis of guaiol (2) (48) represents another example of such a process and also demonstrated its synthetic applicability.

Several years ago, Marshall and his co-workers reported a stereoselective one-carbon ring expansion sesquence with concomitant γ-butyrolactone formation (49, 50). The procedure involves the construction of cyclopropylcarbinol intermediates such as 46a and 46b from an enone as illustrated in scheme II or from other suitable starting materials, and the acid-induced ring



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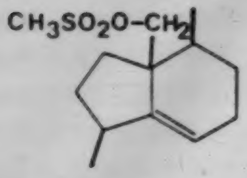
Scheme I



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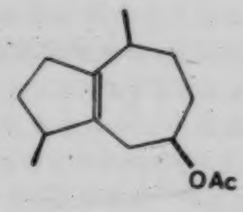

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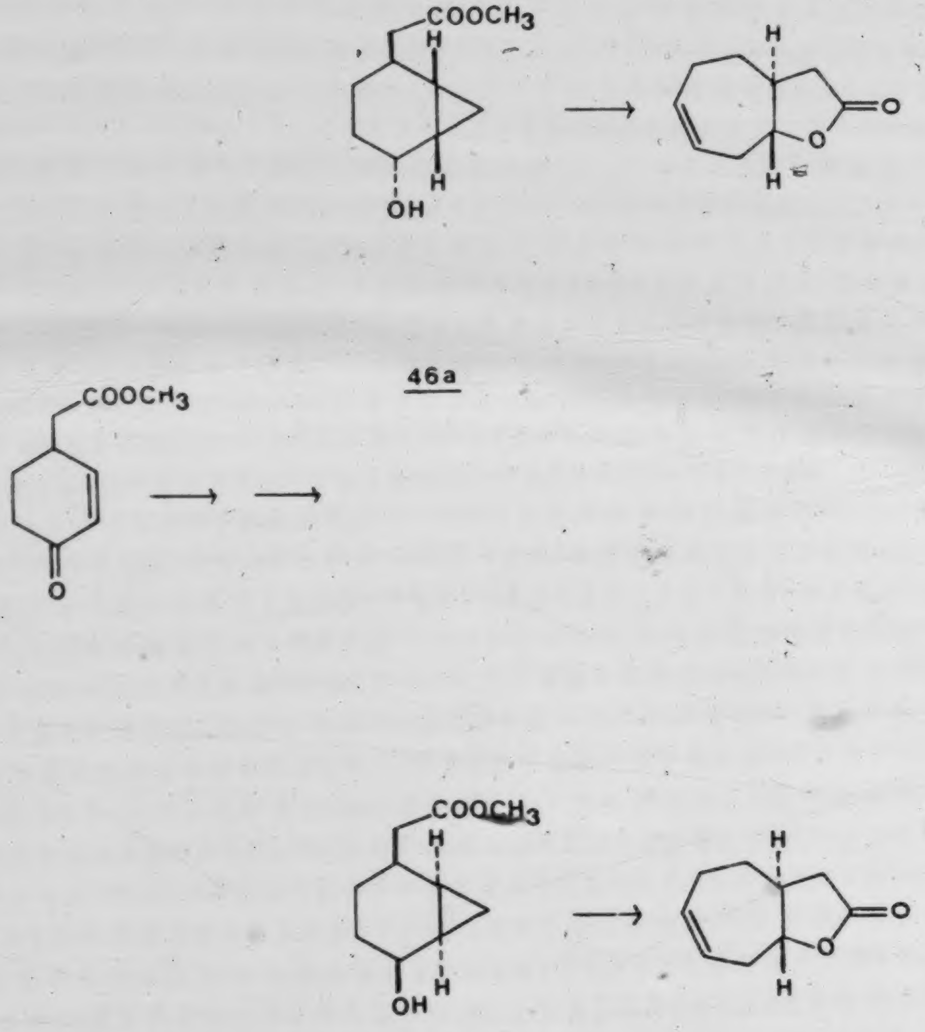
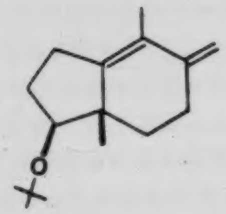


46a

46b

Scheme II



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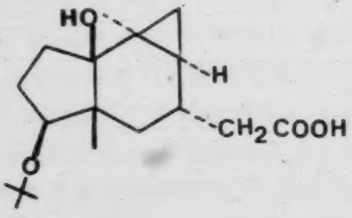

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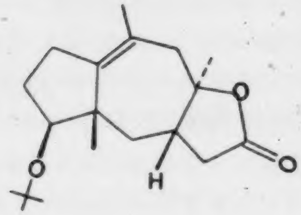
fission of these alcohols to complete the homologation. A modified version of this process has recently been extended to hydroazulene synthesis (51). Thus, the known enone 47 (52) was converted in eight steps into cyclopropylcarbinol 48, which on acid treatment gave rise to hydroazulenic lactone 49. Further modification of the latter substance completed a total synthesis of comferin (14) (51).

(ii) Olefin cyclization reactions.

Cation-initiated transannular cyclization of cyclodecadiene derivatives has been considered to play an important role in the biosynthesis of hydroazulenic sesquiterpenes (17). Several methods for hydroazulenes synthesis have been developed mimicking the possible biosynthetic process. It is noted that the cyclization of possible biosynthetic decadiene intermediates such as 50 to hydroazulene skeleton requires an anti-Markovnikoff mode of reaction as depicted in scheme III. Whereas biosynthetically it can well proceed with ease under enzymatic control, such an unfavorable cationic cyclization is at present impractical in the laboratory. It has been shown, however, that the desired mode of cyclization can be facilitated by means of "activation" of one of the double bonds. Brown and Sutherland, for instance, found that mild acid treatment of 51 mainly gave rise to the hydroazulenic products 52 and 53 (53) as a



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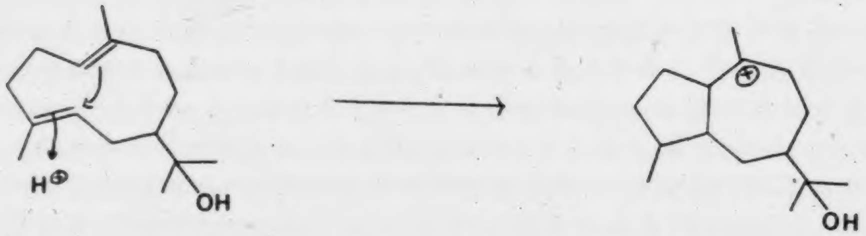

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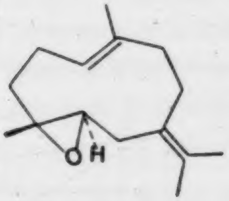
Scheme III



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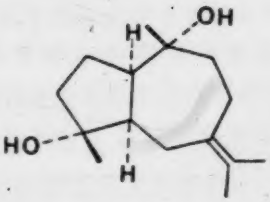
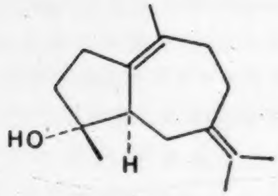


52

result of the acid-promoted epoxide cleavage with transannular participation of the endocyclic double bond. The device used by Marshall, et al., (54) was the introduction of an allylic leaving group to activate the adjacent double bond. This method was exemplified by the solvolysis of cyclodecadiene 54 to 55, a key intermediate in the total synthesis of (±)-globutol (56) (55). Recently, Iguchi and co-workers showed that the guaiazulene skeleton could be obtained by transannular cyclization of germacrane derivative (56). Thus, on treatment with thiophenol and formic acid, germacrone 57 was cyclized to give hydroazulenic ketone 58.

Acid catalized cyclization of appropriately substituted cyclopentane derivatives leading to hydroazulene skeleton has also been extensively studied. Using a Prins reaction, Marshall, et al., have succeeded in cyclizing unsaturated aldehydes 59a and 59b to hydroazulenes 60a and 60b respectively in a highly stereoselective manner (57). An extension of this method is found in a total synthesis of guaiol (2) and bulnesol (33) (58,59), where treatment of 61a and 61b with perchloric acid and acetic anhydride resulted in the formation of, along with 62, the key intermediates 63a and 63b respectively. The use of chloroolefin annelation (60) has been briefly explored in the field of hydroazulene synthesis. The only example known is the



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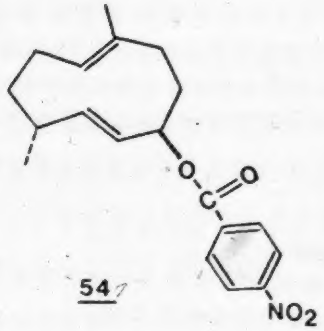

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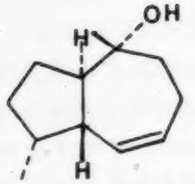

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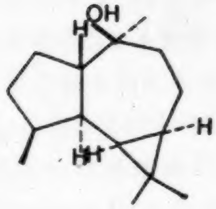

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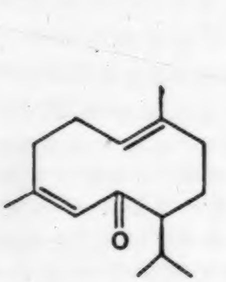

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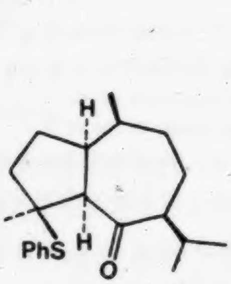

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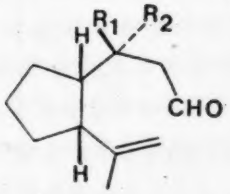
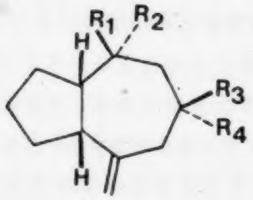


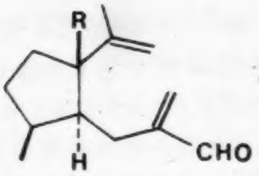
59a: $R_1 = CH_3$; $R_2 = H$

59b. $R_1 = H$; $R_2 = CH_3$



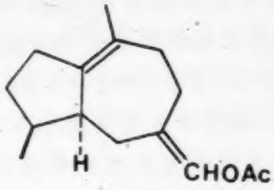
60a: $R_1 = CH_3$; $R_2 = H$
$R_3 = H$; $R_4 = OH$

60b: $R_1 = H$; $R_2 = CH_3$
$R_3 = OH$; $R_4 = H$



61a: R = ---H

61b: R = —H



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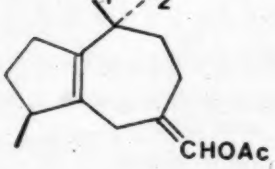
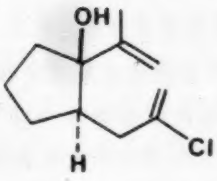


63a: $R_2 = H$; $R_1 = CH_3$

63b: $R_2 = CH_3$; $R_1 = H$



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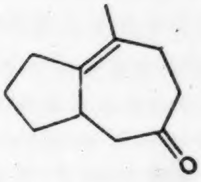
formolysis of olefin 64 to give ketone 65 (61) and its synthetic applicability remains to be attested.

(iii) Selective Ring-opening of Tricyclic Compounds.

In 1965, Stork and Landesman described a two carbon ring expansion procedure (62) involving the reaction of a cycloalkane enamine with acrolein as a starting point. Subsequent treatment of the resulting amino ketone 66 with methyl iodide and alkali induced selective cleavage of a bridge carbon-carbon bond to furnish the unsaturated acid of general formula 67. Some six years later, this method was extended to a hydroazulene synthesis in which amino ketone 68, prepared from pyrrolidine enamine of cyclopentanone and 1-formylcyclopentene, was converted to an acid 69 in an analogous manner (63). An alternative method has also been demonstrated in a total synthesis of guaiol (2) (64) in which the selective ring-opening required for the key transformation 70→71 (with sodium methoxide) is apparently facilitated by the presence of a nonenolizable (between two carbonyls) vinylogous β-diketone moiety.

The third variation in this category is in close association with the present work and is therefore separately discussed in some detail as follows.

In principle, the hydroazulenic system could be produced by cleaving a specific bond of an appropriate tricycle which embodies such a system. One of the conceivable tricycles is represented by formula 72 in which two five-membered rings are attached to a cyclobutane. The transformation of 72 to hydroazulene skeleton could be envisaged by a two-carbon ring expansion process involving selective cleavage of bond a or b of the highly strained cyclobutane ring. The conveyance of this concept to practice has been greatly assisted by the rapid development of photocycloaddition reactions during the past two decades (65). The otherwise difficultly accessible material of type 72 could now be obtained in a remarkably simple fashion by photochemical fusion of two cyclopentene derivatives. The feasibility of such an approach was first demonstrated by Hikino and de Mayo (66). They showed that 3-acetoxy-2-cylcopentenone could add photochemically to cyclopentene to yield tricyclic keto acetate 73 and that the latter compound when subjected to alkali treatment underwent selective ring cleavage through a retroaldol process giving hydroazulenic dione 74. Clearly, such an approach to hydroazulene synthesis is superior to those discussed earlier in terms of simplicity. The complete lack of functionality coupled with the fact that the differentiation of two ketone carbonyls is expected to be difficult, however, make this particular method not viable to the synthesis of hydroazulenic sesquiterpenes.



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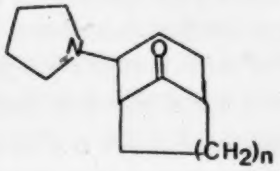

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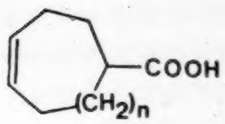

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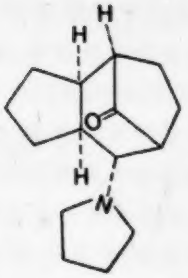

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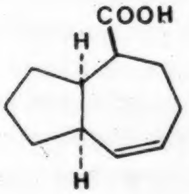

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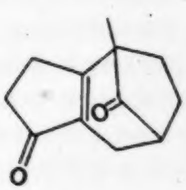

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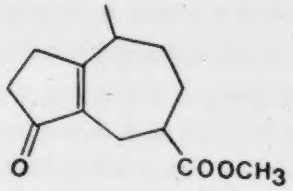

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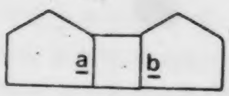

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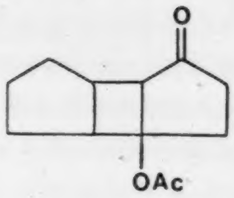

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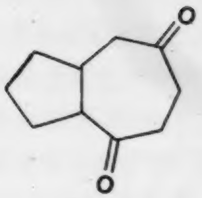

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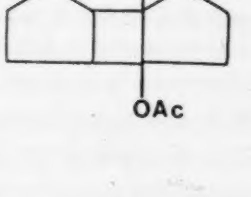

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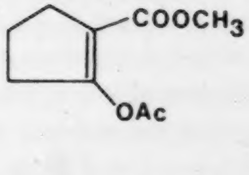

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Based on the same general principle, a new method has been developed in this laboratory (67). This method allows the formation of a hydroazulenic system with functionalities in both rings by two synthetic steps. The tricyclic intermediate 75 was produced with high regioselectivity by photocycloaddition of 2-cyclopentenone to 1-acetoxy-2-carbomethoxycyclopentene (76). The latter compound was chosen for the following reasons. The two substituents were expected to reinforce the regioselectivity of the addition as they were shown to exert opposite orientation effects (64). Their locations in the photoadduct 75 were further expected to permit the cleavage of a specific bond by a reverse Claisen-type reaction to fulfill the required two carbon ring expansion leading to hydroazulene moiety. Indeed, photoadduct 75 when treated with sodium methoxide resulted in the formation of keto ester 77[3]. The two ketone carbonyls could be readily differentiated by taking advantage of the preexisting ketone carbonyl in the tricycle 75. Thus, ketalization of 75 followed by ring fission gave rise to ketal ester 78.

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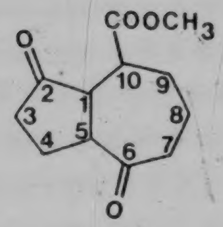
[3] It is noted that although the same general principle applies, this procedure has practical differences from that of Hikino and de Mayo (vide supra). Most noticeably, whereas in the former case the cyclopentanone ring was retained throughout the synthesis, the latter method required its modification to a seven-membered one.

The present studies are focused on the general applicability of this method to the synthesis of guaiazulenic sesquiterpenes using kessane (9) as a model. The following sections describe a highly stereoselective total synthesis of a hitherto unknown epimer of kessane (9), namely, 5-epikessane (79), and two unsaturated derivatives, dehydrokessane (80) and Δ^5-dehydrokessane (81) by a modified version of the method.



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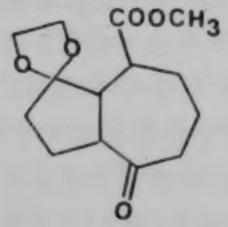

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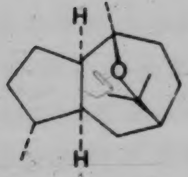

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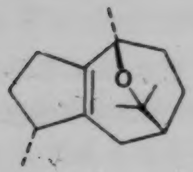

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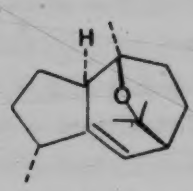

81

RESULTS AND DISCUSSION

It is readily noticeable that keto ester 77, the end product of the reported method (67), resembles kessane (9) by the presence of the parent hydroazulene framework and a potential methyl substituent at C-10[4] position. Furthermore, its C-6 ketone carbonyl could serve as a convenient handle for the incorporation of an isopropyl unit required for kessane (9) at C-7, as well as for the adjustment of the stereochemistry, if necesary, of the two adjacent centers C-5 and C-7 (and hence C-10 through the ether bridge formation) by epimerization at a suitable stage. In order to utilize the method effectively in the synthesis of 9, however, the following requirements have to be met: (i) activation of C-4 so that a methyl group could be introduced, preferably in a highly stereoselective manner, and (ii) oxidation of C-10 to an adequate level to assist the required ether ring formation. It was with these objectives that the present studies were commenced.

To facilitate the incorporation of the required methyl group at C-4, 4-acetoxy-2-cyclopentenone (68) was chosen as the starting enone for the photocycloaddition reaction with 1-acetoxy-2-carbomethoxycyclopentene (76). The photoadduct was expected to undergo facile β-elimination reaction to generate an α,β-unsaturated ketone moiety thereby providing a mechanism for introducing a methyl group through a conjugate addition. Irradiation of 4-acetoxy-2-cyclopentenone and and (76) in benzene using a 450 W Hanovia high-pressure mercury-vapor lamp and a Pyrex filter at room temperature for 24 h, gave rise to a mixture consisting of at least three components (disregarding the possible stereoisomerism due to the unspecified chiral centers), the desired ketone 82 as the major product and the diastereomeric ketones 83 and 84 in minor quantities. These photoadducts could not be isolated in pure form due to their instability. Attempted purification of the crude mixture by silica gel column chromatography, for instance, induced, in part, elimination of acetic acid. The tentative structural assignments were made on the basis of the subsequent transformations carried on with the unpurified mixture.

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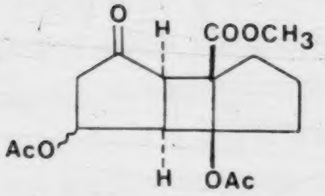
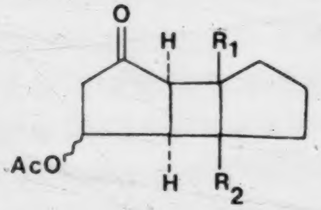
[4] In this section, the conventional numbering system for hydroazulene as indicated in formula 77 is used.

The crude photoadducts when treated with a catalytic amount of p-toluenesulfonic acid at room temperature underwent smoothly β-elimination of acetic acid. Although homogeneous on thin-layer chromatography (tlc), the material thus obtained in 80% yield (based on 4-acetoxy-2-cyclopentenone) in fact consisted of three components as shown by the gas chromatographic (gc) analysis and by the proton nuclear magnetic resonance (^{1}H nmr) spectrum which showed three singlets each for the acetoxy (δ 1.86, 1.92, and 2.00) and the carbomethoxy (δ 3.52, 3.56, and 3.65) groups as well as three multiplets each for the α- (δ 6.33, 6.30, and 6.24) and the β- (δ 7.36, 7.60, and 7.78) protons of the enone moiety. Furthermore, by the relative intensities of these signals the ratio of the three components could be determined to be approximately 7:3:1. Although, the mixture was found to be inseparable by column chromatography, a small amount of each of the two main components could be obtained in pure form by means of high pressure liquid chromatography. These two compounds were shown to possess the gross structure 85 by the following spectral data. The by-far major compound showed, in its infrared (ir) spectrum, characteristic absorption bands for the ester carbonyls and the α,β-unsaturated cyclopentenone at 1740 and 1715 cm^{-1} respectively. It's ^{1}H nmr displayed two methyl singlets at δ 1.92 and 3.52 respectively for the acetoxy and carbomethoxy groups. The olefinic proton α to the ketone was found to resonate at δ 6.33 as a doublet of doublets, while the β-proton appeared at δ 7.36 also as a doublet of doublets. The ir spectrum of the other pure substance showed close similarity to that of the previous one. Two diagnostic carbonyl absorptions were

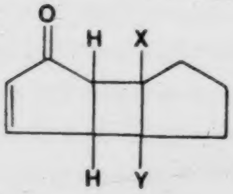


82



83: $R_2 = -COOCH_3; R_1 = -OAc$

84: $R_2 = --COOCH_3; R_1 = --OAc$

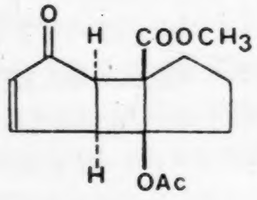


85: $X,Y = COOCH_3; OAc$

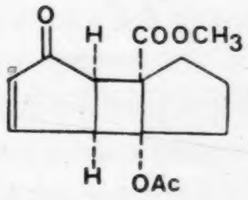
also observed at 1740 and 1715 cm^{-1} for the esters and the α,β-unsaturated cyclopentenone. In the ^{1}H nmr spectrum the acetoxy and carbomethoxy methyl singlets appeared at 1.86 and 3.56 respectively, while the two olefinic protons resonated at δ 6.24 (α-proton) and 7.78 (β-proton) both as a doublet of doublets. Although in the mass spectrum neither of these compounds showed a parent peak, their elemental analyses were both in agreement with a molecular composition of $C_{14}H_{16}O_5$ as required for 85. Although the minor component could not be isolated in pure form, its gross structure could also be deduced to be 85 as the ^{1}H nmr spectrum of the mixture (*vide supra*) showed a third set of signals consisting of two methyl singlets for the acetoxy and carbomethoxy groups as well as two doublets of doublets diagnostic for conjugated enone protons. The fact that the mixture as a whole analyzed satisfactorily for $C_{14}H_{16}O_5$ was also in support of its structural assignment.

In principle, the described reaction sequence could lead to a total of four isomeric compounds 86a, 86b, 87a and 87b (*trans* fusion of bicyclo[3.2.0]heptane is sterically forbidden) differing from each other in either orientation (head-to-tail or head-to-head with respect to the ketone carbonyl and the acetoxy group) or stereochemistry (*syn* or *anti* regarding the two cyclopentane rings) or both. Although it was highly desirable to pin down the exact structure of the three compounds obtained, in particular, the relative orientation of their functionalities, the information available at this stage did not allow us to make unambiguous assignments. The situation was completely clarified only when further synthetic steps were undertaken. To facilitate the discussion, however, the structures so concluded, i.e. 86a, 87a, and 87b for the major, the second major and the minor isomers respectively are used.

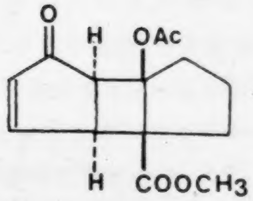
Treatment of 86a at 0°C with a complex prepared from methylmagnesium bromide and cuprous iodide (69) effected the conjugate addition of a methyl group to give ketone 88 in 56% yield. The structure of 88 could be readily deduced from its spectral data. The ir spectrum showed a broad and intense absorption band at 1745 cm^{-1} for the esters and cyclopentanone carbonyls as well as the complete absence of the conjugated enone absorption at 1715 cm^{-1} previously observed for its precursor. In the ^{1}H nmr spectrum a doublet at δ 1.07 for the newly introduced methyl group and two singlets at δ 1.98 and 3.60 respectively for the acetoxy and the carbomethoxy methyls were observed. A molecular ion peak was recorded at 280.1310 in the mass spectrum in agreement with the required



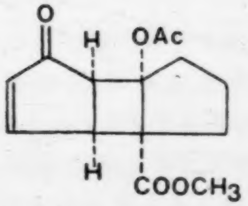
86a



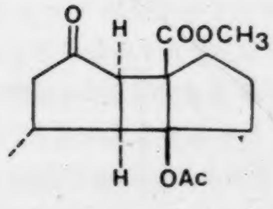
86b



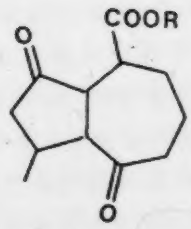
87a



87b



88



89: R = H

90: R = CH_3

formula of $C_{15}H_{20}O_5$. The 1,4-addition reaction was found to proceed with complete stereoselectivity. No detectable amount of the epimeric compound was obtained. Although the mechanism of conjugate addition of "ate" complexes to enones remains to be ascertained, a large number of examples (70) studied indicated that, whenever applicable, the reaction occurs from the sterically less hindered side of the molecule. Based on these observations, the stereochemistry of the newly introduced chiral center in 88 could be depicted as a result of the expected preferential attack of the reagent from the vertex face of 86a.

At this point, ketone 88 was subjected to ring cleavage reaction in an attempt to ascertain the relative orientation of its functionalities which was of crucial importance to the present work. Treatment of 88 with 4 N aqueous sodium hydroxide in methanol at reflux for 24 h followed by esterification of the resulting keto acid 89 with potassium carbonate and methyl iodide in acetone (67) gave rise to the crystalline diketone 90, mp 128-129°C, in 72% yield. The structural assignment[5] was in full agreement with the following spectral data. The ir spectrum displayed absorption bands at 1740 (cyclopentanone and ester) and 1710 cm^{-1} (cycloheptanone). Furthermore, the comlete absence of any absorption in the 1600-1700 cm^{-1} region clearly indicated that a 1,3-dicarbonyl system was not involved in the molecule. In the ^1H nmr spectrum, a methyl doublet and a carbomethoxy singlet appeared at δ 1.08 and 3.72 respectively. The assigned structure was further confirmed by the mass spectrum which showed a molecular ion peak at 238.1212 in accord with the molecular formula $C_{13}H_{18}O_4$.

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[5] Its stereochemistry remains to be determined.

The ring-opening to give a 1,4-diketone 90 rather than a β-diketone 91 or a dione 92 (by a retro-aldol process), which would have been formed should the locations of the acetoxy and carbomethoxy grops in the starting material be reversed, clearly indicated the position of the functionalities in 88 as well as those of its precursors 82 and 86a as depicted. These structural assignments were further substantiated when 88 was reduced with sodium borohydride at 0°C in methanol. Two products were obtained. The major one isolated in 67% yield was readily identified as lactone 93, mp 135-136°C, showing in its ir spectrum the characteristic γ-lactone absorption at 1765 cm^{-1} and an acetoxy band at 1738 cm^{-1}. The ^1H nmr spectrum displayed a doublet of doublets at δ 4.97 due to the methine proton adjacent to the lactone oxygen atom. The structure of the minor product 94 (25% yield;

single isomer; mp 143-145°C) was also evident from its spectral properties. Its ir spectrum exhibited absorption bands at 3600 and 3450 cm^{-1} for the hydroxy group, and at 1735 cm^{-1} for the ester function. In its ^{1}H nmr spectrum, in addition to a methyl doublet at δ 1.00 and an acetoxy singlet at δ 2.04, two low-field signals were also observed; the singlet at δ 5.40 could be readily attributed to the methine proton adjacent to the hydroxy group and the doublet of doublets at δ 4.80 to the hydrogen atom on the other carbon bearing the ether linkage. The two compounds were apparently formed by preferential hydride attack from the sterically less hindered side of 88 followed by lactonization and partial reduction of the lactone ring thus formed[6] (Scheme IV). In addition to confirming the previous structural assignments, the isolation of 93 and 94 further indicated an anti relationship for the two five-membered rings present in 87 (consequently those in the precursors) since the lactone ring formation is not sterically feasible for the corresponding syn isomer.

Having the structure of 88 fully established, it was desirable to remove its ketone carbonyl at this stage while the skeleton was rigid in order to preserve the elaborated cis relationship between the methyl group and the ring juncture hydrogen atom α to the ketone required for kessane (9) synthesis. Treatment of 88 with 1,2-ethanedithiol in the presence of boron trifluoride etherate afforded an 84% yield of the corresponding thioketal 95 which showed a diagnostic absorption band at 1735 cm^{-1} in the ir spectrum for the two ester carbonyls. The presence of a thioketal group was verified by the ^{1}H nmr spectrum which displayed a four-proton multiplet centered at δ 3.20. A molecular ion peak at 356.1117 in the mass spectrum was in agreement with the required formula of $C_{17}H_{22}O_4S_2$.

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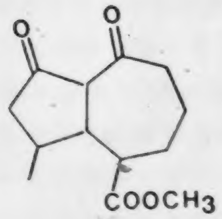
[6] Although reductions of esters and lactones with sodium borohydride are uncommon, several examples are known. For a leading reference, see ref. 71.

While enone 86a was subjected to the foregoing investigation, the structure of 87a was also being examined. These findings are now needed to be discussed. Under conditions similar to those used in the transformation of 86a → 88, the reaction of 87a with methylmagnesium bromide-cuprous iodide complex gave rise to a 53% yield of a single isomer 96 as a result of the expected exclusive addition of the reagent from the exo side of the cyclopentenone ring. The ir and ^{1}H nmr spectra of 96 were found to be similar to those of 88. Subsequent treatment of 96 with 1,2-ethanedithiol and boron trifluoride etherate resulted in the formation of a mixture of three compounds. One



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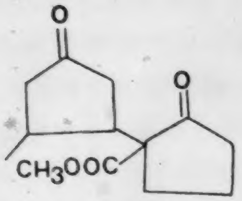
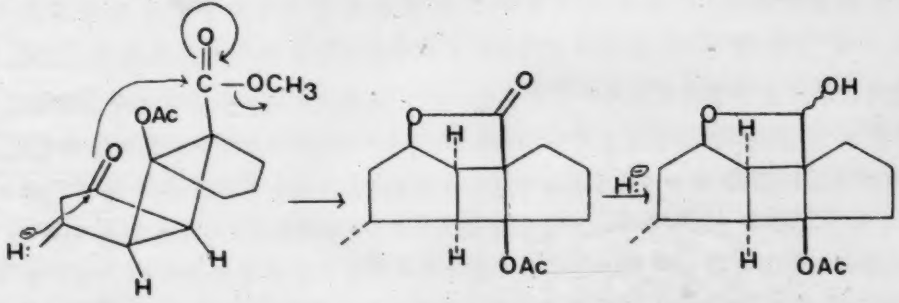


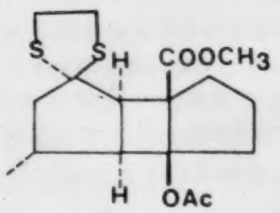
92



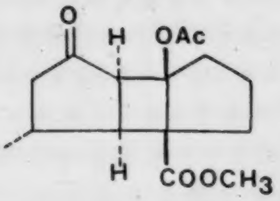
93

94

Scheme IV

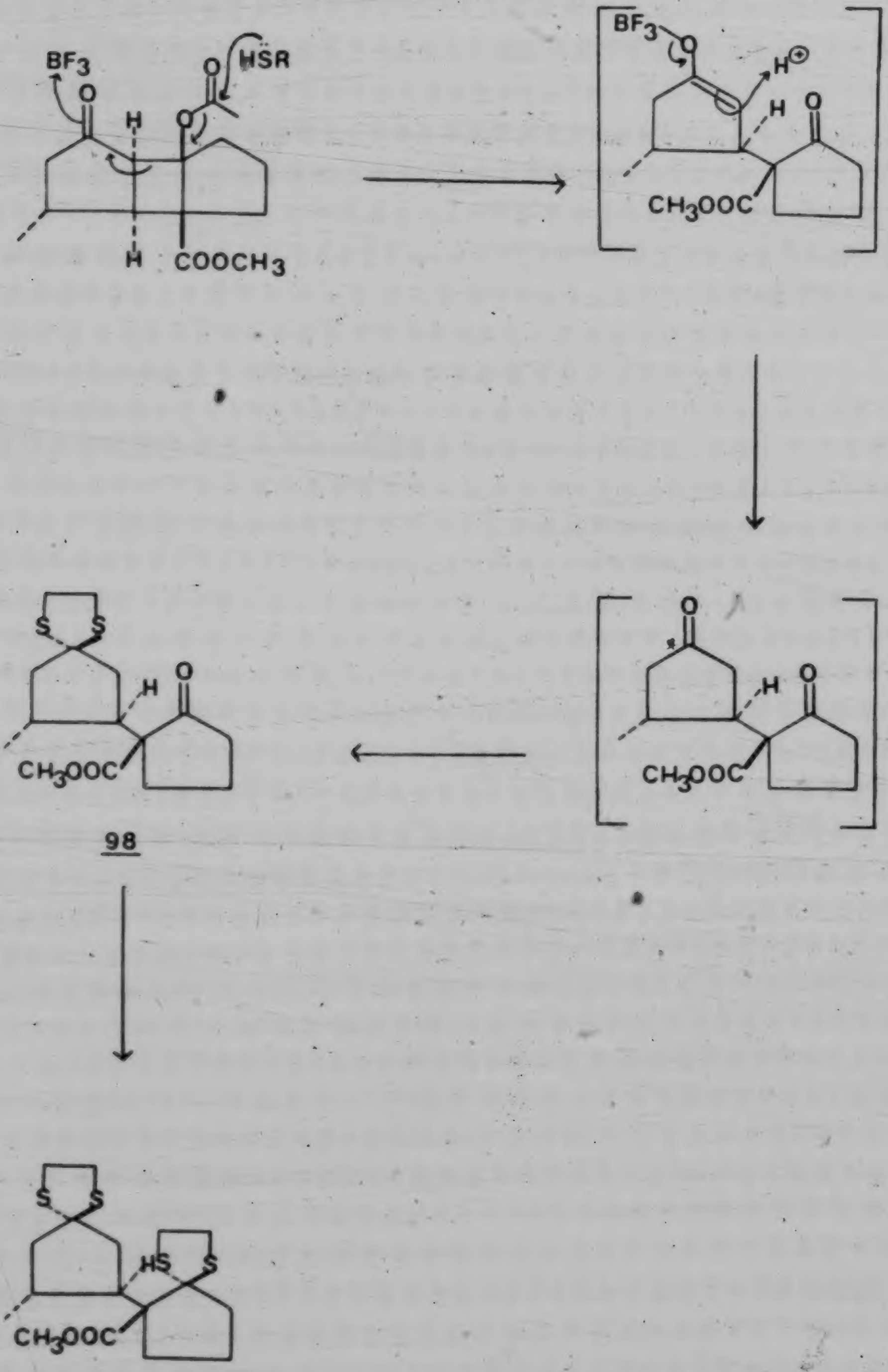


95



96

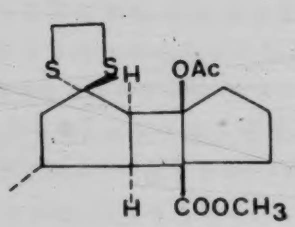
of which was readily identified as the corresponding thioketal 97 where ir and mass spectra were shown to be similar to those of 95. In the ^{1}H nmr spectrum, two methyl singlets at δ 1.98 (acetoxy) and 3.57 (carbomethoxy), a methyl doublet at δ 1.19 and a four-proton singlet at δ 3.14 for the thioketal methylenes were observed. The other two compounds were found to be ring cleavage products, possessing structures 98 and 99 respectively. The ^{1}H nmr spectrum of 99 displayed a methyl doublet at δ 1.16 and a carbomethoxy singlet at δ 3.20 but the absence of any acetoxy signal. In the same spectrum, an eight-proton singlet was also observed at δ 3.68 strongly suggesting that two thioketal groups were present. The presence of an ester group was confirmed by the ir spectrum which showed an absorption band at 1725 cm^{-1}. Furthermore, its molecular composition of $C_{17}H_{26}O_2S_4$ was in accord with the mass spectrum showing an molecular ion peak at 390.0805. Compound 98 showed, in the ir spectrum, in addition to an ester carbonyl band at 1725 cm^{-1}, an intense absorption at 1750 cm^{-1} characteristic for a five-membered ring ketone. In the ^{1}H nmr spectrum, a methyl doublet, a thioketal singlet and a carbomethoxy singlet were observed at δ 0.93, 3.20 and 3.60 respectively, however the methyl signal corresponding to an acetoxy group was again absent. This information allowed its partial structural assignment with only the location of the thioketal group uncertain. This aspect was readily clarified by the mass spectrum which showed, other than the required molecular ion peak at 314.1002, a base peak at 173.0454 corresponding to an ion fragment of $C_8H_{13}S_2$ of which the structure of 100 was most probable. The structure of 98 was further confirmed by hydrolysis with mercuric chloride in aqueous acetonitrile to give dione 101 whose ir and ^1H nmr spectra were in accord with the depicted structure. The mass spectrum displayed molecular ion peak at 238.12099 and a base peak at m/e 142 corresponding to $C_7H_{10}O_3$ attributed to fragment 102 by a Mclafferty fragmentation (72). In addition, a peak at m/e 97 most likely due to fragment 103 was in support of the assigned location of the thioketal group in the immediate precursor. Plausible fragmentation pathways are depicted in Scheme VI. Although rather unexpected, the formation of 98 and 99 could be rationalized by invoking an acid catalyzed retro-aldol reaction followed by thioketalization of the dione intermediate (Scheme V). More importantly, the conversion of 96 into these two compounds clearly indicated the relative orientation of its functional groups as formulated and this formulation could be logically extended to the precursors 83 and 87a. Re-



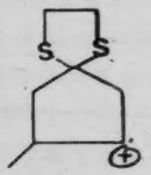
98

99

Scheme V



97



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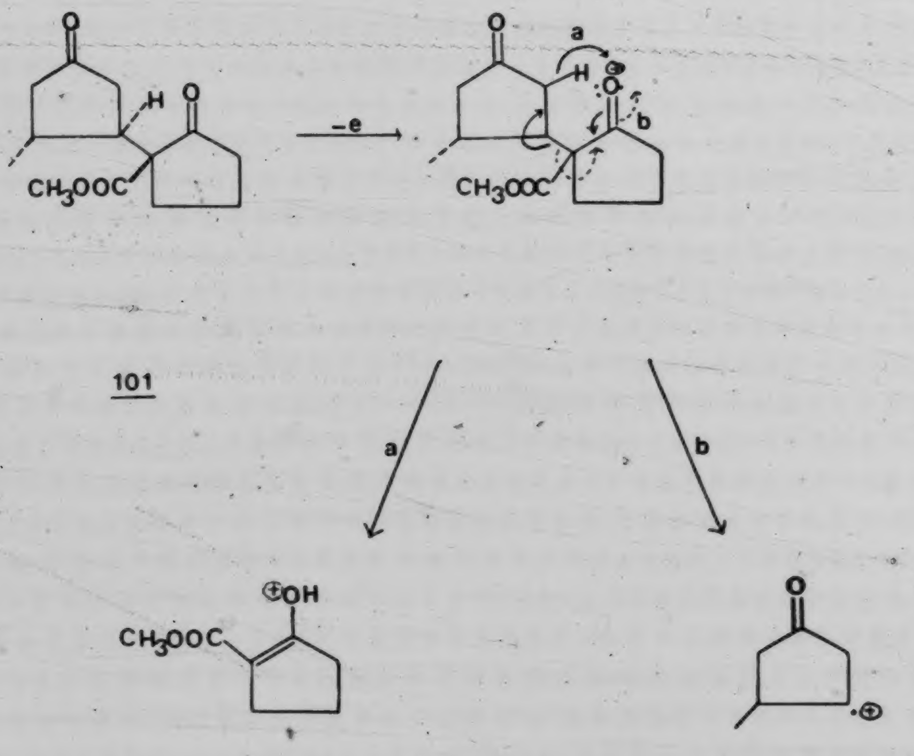


101

102

103

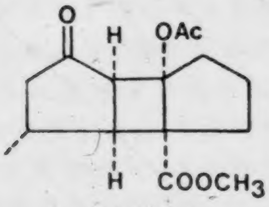
Scheme VI

garding the stereochemistry of these compounds, no solid evidence has thus far been obtained. The anti arrangement was tentatively assigned on the basis of the known preferential formation of the anti isomer when two cyclopentane molecules were fused photochemically (65a). An immediate precedent was that, of the pair 82 and its syn-isomer possessing the head-to-tail orientation, the former was produced predominantly (possibly to an exclusive extent) as reflected in the isolation of 86a as the major product upon elimination. Thus, the predominence of the anti-isomer in the head-to-head pair 83 and 84 could be assumed.

The structural elucidation was rather demanding at the early stage of the present studies. The synthesis of the desired tricyclic intermediate was in fact simple; only four steps (photocycloaddition, elimination, 1,4-addition and thioketalization) were required and 95 was obtained in satisfactory yield with good control of stereochemistry. Its large scale preparation was further facilitated by the fact that the separation of the mixture 86a, 87a and 87b, which was only partially successful and laborious as noted previously, was unnecessary. Thus, when the mixture was subjected to the treatment with methylmagnesium bromide-cuprous iodide a 65% yield of a mixture of 88, 96 and a third compound was obtained. The latter compound was apparently derived from 87b and to which the structure 104 (the orientation of the functional groups in both 87b and 104 remained to be determined at this stage) could be assigned. It was evident from the ^1H nmr spectrum of the mixture that, in addition to the signals corresponding to 88 and 96, a methyl doublet (δ 1.12), an acetoxy singlet (δ 1.98) and a carbomethoxy singlet (δ 3.66) were observed. The ^1H nmr spectrum further indicated the ratio of 88, 96 and 104 was *ca*. 7:3:1 similar to that of the starting enone. The mixture (homogeneous on tlc) without separation was subsequently treated with 1,2-ethanedithiol and boron trifluoride etherate. A total of five compounds were obtained, four of them were conveniently separated and were found to be identical respectively with 95 (47% yield), 97 (1%), 98 (13%) and 99 (17%). The fifth component was not obtained in pure form but along with 95 as a *ca*. 1:1 mixture (6%). The new compound was obviously the *syn*-isomer of either 95 or 97 as the ^1H nmr spectrum of the mixture showed two sets of signals; one of which corresponded to 95 and the other contained a methyl doublet at δ 1.19, and three signlets at δ 1.91 (acetoxy), 3.28 (thioketal), and 3.62 (carbomethoxy). Its chemical correlation with 97 in a later stage (see footnote 7 on page 53) revealed its structure of 105 and further ascertain those of its precursors as formulated.

Having assigned the structure of the desired tricyclic compound 95 and secured its preparation in large quantity, our immediate concern was to generate the seven-membered ring. It was noted earlier that in order to facilitate the formation of a bridged ether linkage required for kessane (9), an adequate oxidation level of the carbon presently bearing the carbomethoxy group was highly desirable. An exceedingly attractive scheme called for the transformation of 106 → 107 using a Grob fragmentation (73). This process would not only provide simultaneously the hydroazulene system and a desirable oxidation level for the carbon in question, but also simplified the necessary modification of the carbomethoxy group into a methyl. Toward this end thioketal 95 was heated at reflux with lithium aluminum hydride in tetrahydrofuran. The diol 106 thus obtained in 69% yield showed in the ir spectrum a hydroxy absoprtion band at 3480 cm^{-1} and in the ^{1}H nmr spectrum a methyl doublet at δ 1.22 and two singlets at δ 3.12 and 3.70 for the thioketal methylenes and methylene protons α to the hydroxyl group. Attempted monotosylation of 106 with one equivalent of p-toluenesulfonyl chloride in pyridine either at 0°C or at room temperature resulted in complete recovery of the starting material. When the reaction mixture was refluxed, however, a new alcohol was obtained in 58% yield as the sole product, and the following spectroscopic analysis revealed its structure of 108 possessing a novel ring system. The ir spectrum displayed an absorption band at 3500 cm^{-1} indicating the presence of a hydroxy group. In the ^1H nmr spectrum, a four-proton multiplet centered at δ 2.85 and a two-proton singlet at δ 2.70 were observed for the methylene hydrogen atoms adjacent to the sulfur atoms. A methyl doublet at δ 0.90 and another doublet at δ 5.78 attributed to the olefinic proton were also recorded. A molecular ion peak at 256 in the mass spectrum was in agreement with the depicted structure. The involvement of a monotosylate species in the formation of 108 was apparent. The exclusive participation of a sulfur atom leading to 108 through hypothetical steps shown in Scheme VII, was undoubtedly due to the close proximity of this atom and the carbon bearing a leaving group. Indirectly, it might be also partly due to the fact that the expected Grob fragmentation was suppressed by the steric congestion of the thioketal and the *p*-toluenesulfonoxy group which disfavored the latter to adopt a conformation *anti*-periplanar to bond *a* required for such a process.

A remedy to circumvent the encountered difficulties was obviously the removal of the thioketal moiety in advance. Reduction of 106 with Raney-nickel was, how-



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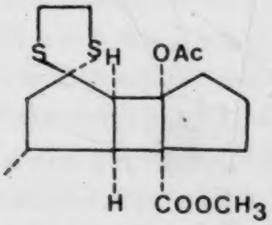

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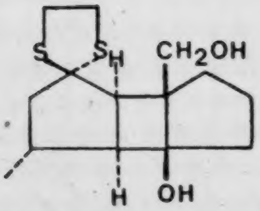

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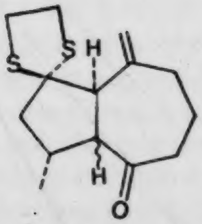

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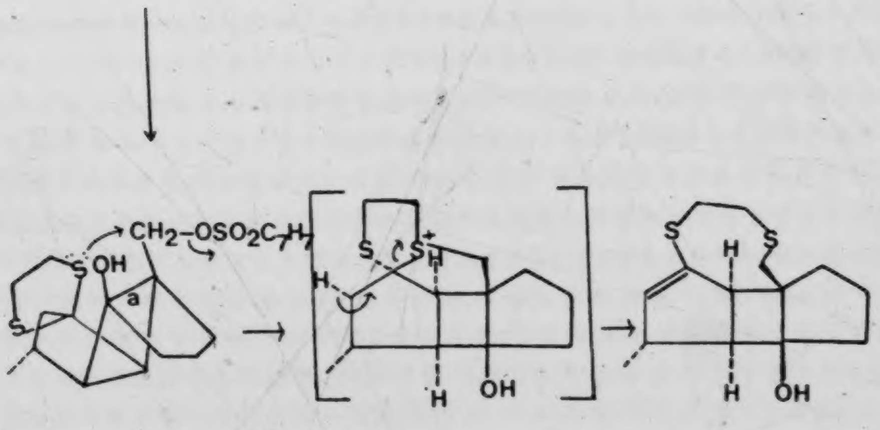
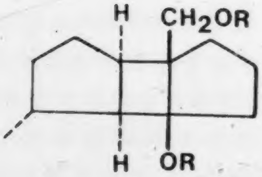


108

Scheme VII

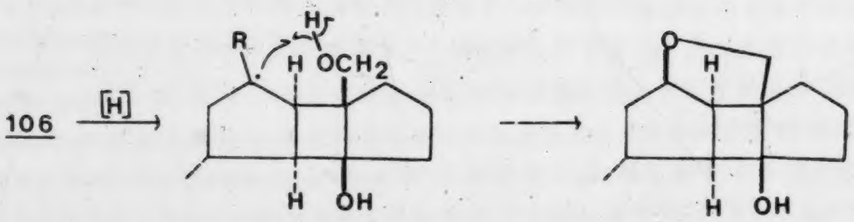
ever, equally unsuccessful. The crystalline product, mp 71-72°C, obtained in 76% yield was found to be not the anticipated diol 109 but hydroxy ether 110 which showed hydroxy (3480 cm^{-1}) and ether (1110 cm^{-1}) absorption bands in the ir spectrum. In the ^1H nmr spectrum, two doublets at δ 3.26 and 3.67 could be attributed to the methylene protons of the ether ring and a doublet of doublets at δ 4.25 to the methine proton adjacent to the oxygen atom. Mechanistically, the formation of 110 is far from clear. The pathway depicted in Scheme VIII serves merely as a convenient explanation.

As a consequence of the above findings, our attention was turned to the desulfurization of 95. Its reaction with W-2 Ra-Ni in refluxing ethanol gave 62% yield of the desired ester 111 showing in the ir spectrum a diagnostic absorption band for the ester-carbonyls at 1735 cm^{-1}. In its ^1H nmr spectrum, the resonance due to the thioketal protons was absent and a methyl doublet at 0.92 and two singlets at δ 3.54 and 1.95 for the carbomethoxy and the acetoxy groups respectively were observed. Although the compound did not give a molecular ion peak in the mass spectrum, its composition was consistent with the elemental analysis. Two by-products 112 and 113 were also obtained (30% yield) as a mixture in ca. 1:1 ratio. Their structures



109 : R = H

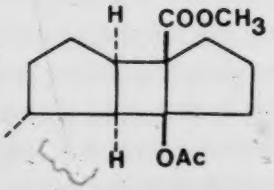
109a: R = D



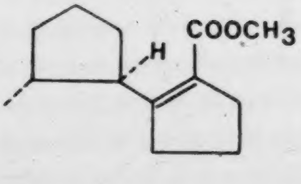
R = H ; SCH_2CH_3; SCH_2CH_2SH

110

Scheme VIII



111



112

were deduced on the basis of the following spectral data. The mixture displayed in the ir spectrum two carbonyl absorptions at 1735 and 1710 cm^{-1} indicative of the presence of a saturated ester and an α,β-unsaturated ester. In the ^1H nmr spectrum, a methyl doublet (δ 0.91), a carbomethoxy singlet (δ 3.54) and another carbomethoxy singlet (δ 3.60) were integrated to a ratio of 2:1:1 and the resonance corresponding to an acetoxy methyl was not observed. Two equally intense molecular ion peaks at 208 and 210 in the mass spectrum further substantiated the structural assignments. Mechanistically, their formation could be rationalized as shown in Scheme IX by generating a free radical intermediate followed by the collapse of such a species involving the ejection of an acetoxy radical. Although details of the mechanism remain to be ascertained, one important aspect was clear: the by-products must be formed at the expense of the desired ester 111. A number of attempts were made to suppress their formation using different grades of Ra-Ni, temperature, and solvents but no complete success has so far been achieved.

Lithium aluminum hydride reduction of 111 proceeded smoothly to give a near-quantitative yield of crystalline diol 109, mp 86-87°C, the hydroxy absorption appeared in the ir spectrum at 3500 cm^{-1}. The ^1H nmr spectrum displayed a methyl doublet at δ 0.86 and two one-proton doublet of doublets at δ 3.44 and 3.86 for the hydrogen atoms α to the hydroxy group. The chemical nonequivalence of these two germinal protons could be a result of intramolecular hydrogen-bonding of the hydroxy groups, which was also suggested by the ir spectrum. In the mass spectrum a molecular ion peak was not recorded due to its ease of losing a water molecule to give a fragment of m/e 178 which was found to be the base peak.

A 1,3-glycol cleavage was subsequently carried out on 109 for the generation of the required hydroazulene skeleton. Diol 109 was treated with p-toluenesulfonyl chloride in pyridine at room temperature for 18 h. Under these conditions, it afforded an 83% yield of the keto olefin 114, mp 32-34°C, as a result of concomitant tosylate formation and fragmentation.[7] The ir spectrum of 114 showed absorption bands at 1710 (ketone), 3090, 1645 and 900 cm^{-1} (carbon-carbon double bond). In the ^{1}H nmr spectrum, a methyl doublet at δ 0.96 and two doublets for the olefinic protons at δ 4.76 and 4.80 were consistent with the formulation which was further confirmed by the mass spectrum showing a molecular ion peak at 178.1358. The sharp spectral peaks and its observed homogeneity in tlc coupled with the narrow melting range were suggestive of a single stereoisomer of 114. Since complete epimerization of the chiral center α to the ketone was highly unlikely under the mild conditions used, a *cis* ring juncture could be assigned. Experimentally, this was proven as follows. Fragmentation of deuterated diol 109a prepared from 109 by deuterium exchange was carried out under the same conditions as before. The product thus obtained was shown by mass spectrum to be free of deuterium atom. These results strongly suggested that epimerization was not induced during the transformation. It follows that keto olefin 114 was formed with retention of the stereochemistry of the starting material. In fact 114 was shown to be thermodynamically more stable than the *trans*-isomer which remains unknown. Attempted epimerization of 114 with sodium methoxide (prepared from sodium hydride and methanol) in methanol at reflux did

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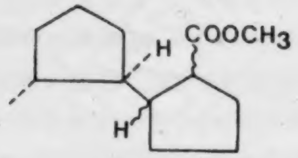
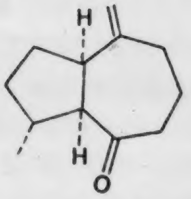
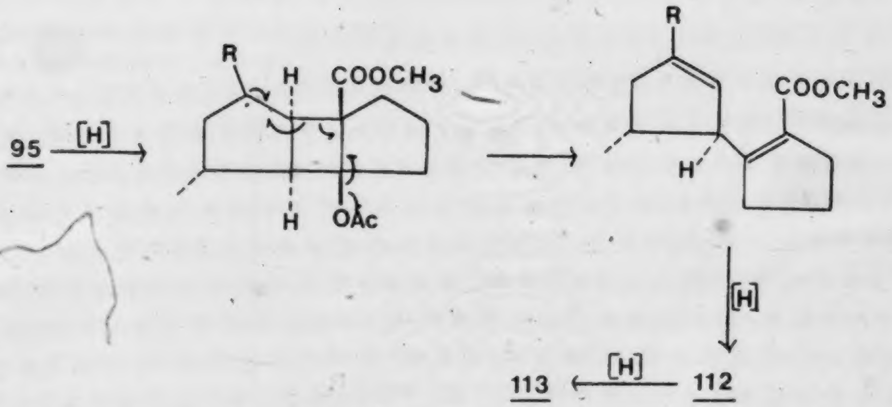
[7] Under similar conditions to those used for the transformations 95→111→109→114, desulfurization of 97 with Ra-Ni followed by lithium aluminum hydride reduction of the resulting ester 115 gave rise to diol 116 which on treatment with p-toluenesulfonyl chloride in pyridine underwent fragmentation to give the isomeric keto olefin 117. When the same reaction sequence was applied to the mixture of 95 and 105 obtained previously, keto olefin 114 and 117 were obtained. These findings strongly suggested a diastereomeric relationship of 97 and 105 and the structure of the latter as such.



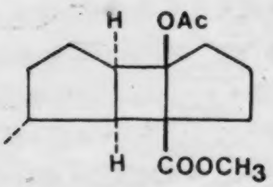
113



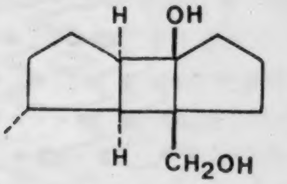
114



Scheme IX



115



116

not give rise to any detectable amount of the latter isomer.

The conversion of 114 to kessane skeleton requires two major operations: the introduction of an isopropanol substituent to C-7 and the formation of an ether ring. The former was achieved by the following two synthetic steps. Keto olefin 114 was converted into keto ester 118 using sodium hydride and dimethyl carbonate. The product thus obtained in 93% yield was shown by the ir spectrum [3450 (hydroxy), 1745, 1710 (ester and ketone), 1600 (enol double bond), 3095, 1645 and 900 cm^{-1} (double bond)] to exist partially in the corresponding enol form 118a. The ^1H nmr displaying two methyl doublets at δ 0.97 and 1.05 as well as two carbomethoxy singlets at δ 4.74 and 4.85 was in support of the tautomeric nature as well as the structural assignment. Due to the complication arising from the rapid tautomerization, the stereochemistry of 118 could not be secured with certainty. Subsequent treatment of the anion of 118 generated by sodium hydride with excess methyllithium (74) resulted in the formation of ketol 119 in 57% yield. The product exhibited in the ir spectrum an absorption band at 3500 cm^{-1} indicative of an intramolecularly hydrogen-bonded hydroxy group. Characteristic absorption bands were also found for the double bond (3100, 1645, 900 cm^{-1}), the ketone carbonyl

(1695 cm^{-1}) and the gem-dimethyl moiety (1365 and 1380 cm^{-1}). In the ^{1}H nmr spectrum, in addition to a methyl doublet at δ 1.00 and a singlet at δ 4.30 for the two olefinic protons, the two methyls of the isopropanol group appeared as two singlets at δ 1.06 and 1.11. Their chemical nonequivalence could be attributed to a hydrogen-bonding between the hydroxyl group and the ketone carbonyl as also suggested by the ir spectrum. The mass spectrum displaying a molecular ion peak at 236.1771 was in full support of the structure formulated. The stereochemistry of 119 was deduced on the basis of the following considerations. By selective decoupling, the C-15 carbon of 119 was shown to resonate in the ^{13}C nmr spectrum[8] at 20.4 ppm, a downfield shift of 0.6 ppm from 19.8 ppm which was observed for the corresponding atom in 114. The observed small difference in chemical shifts suggested that the conversion of 114 to 119 was not accompanied by a major change in geometry, since a change of cis ring juncture to a trans one is necessary to bring C-4—C-15 and C-5—C-6 bonds into parallel or near parallel and consequently a large upfield shift of the carbon atom in question is expected due to γ-gauche effect (75). With respect to the stereochemistry of C-7, no spectroscopic evidence was available to allow its assignment without ambiguity. However, since this chiral center was generated through a kinetically controlled process, i.e. protonation of the intermediate enolate ion right before the work-up of the reaction, it could be assigned tentatively on the basis of the expected preferential attack of acid from the sterically less hindered side.

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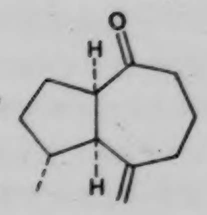
[8] ^{13}C nmr spectra of compounds 114, 119, 121, 123, 79 and 9 are compiled in Fig. 1 for comparison.

Acid catalyzed cyclizations of unsaturated alcohols to five- or six-membered ring ethers have been well documented (76). Initial efforts made to cyclize 119 using trifluoroacetic acid and hydrochloric acid under a variety of conditions were fruitless. Equally unsuccessful was the attempted iodo ether formation (77), using iodine and potassium iodide. By means of oxymercuration (78), however, the desired cyclization proceeded smoothly. Thus, brief treatment of ketol 119 with two equivalent of mercuric acetate in aqueous tetrahydrofuran (1:1) at room temperature resulted in the complete disappearance of the starting material. The organomercury product 120 without isolation was reduced immediately with sodium borohydride. In addition to a 61% yield (based on the consumed starting material) of the desired keto ether 121, a 34% of starting ketol 119 was recovered. The latter aspect is of some theoretical interest. Since the oxymercuration process, as noted,



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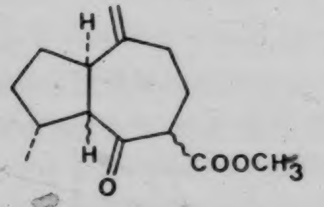
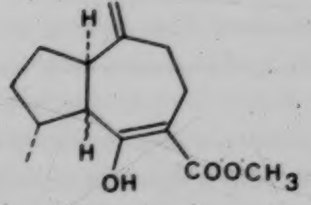
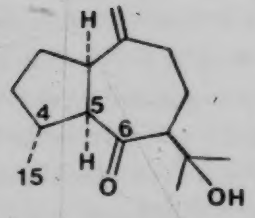


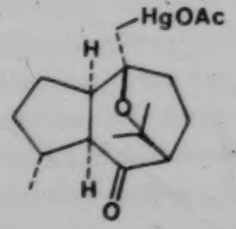
118



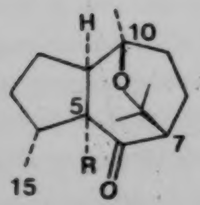
118a



119



120

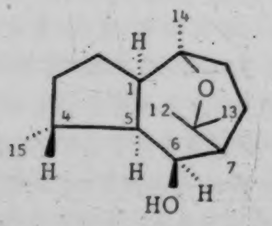


121 : R = H
126 : R = D
127 : R = Br
129 : R = Cl

resulted in the total consumption of the starting material and since variation of reaction conditions did not suppress to a large extent its recovery, it appeared that 119 was generated from 120 by an elimination reaction promoted by a base (hydride or hydroxide ion) during the reduction step. Alternatively, it could have been produced by the reduction of a second species such as 122 formed in competition with the cyclization during oxymercuration. The structure of the desired product 121 could be deduced from its spectral data. In the ir spectrum, it exhibited diagnostic bands at 1705 (ketone), 1095 (ether), 1370 and 1380 cm^{-1} (gem-dimethyl) and the absence of hydroxy absorption. In the ^1H nmr spectrum, a doublet at δ 1.05 and three singlets at δ 1.10, 1.21 and 1.30 were observed for a total of four methyls. In the ^{13}C nmr spectrum, the C-15 carbon appeared at 22.0 ppm and again experienced a small downfield shift from that of its precursor 119 suggesting that the cis ring juncture was intact during the transformation. Although the stereochemistry of C-7 and thus C-10 could not be fully established at this stage, tentative assignment could be made based on the following considerations: (i) Complete inversion of C-7 was highly unlikely under the mild condition used for the transformation. (ii) The initial complex formation required for the oxymercuration reaction which is known to undergo trans addition (79) was likely to involve, in the case of 119, the addition of mercuric acetate to the double bond from the same side of the ring juncture hydrogen atoms to minimize the steric interactions.

In order to ascertain the stereochemistry of 121, it was reduced with lithium aluminum hydride, in near quantitative yield, to the corresponding alcohol 123 which showed a characteristic hydroxy absorption band at 3630 cm^{-1} in the ir spectrum and a molecular ion peak at 238.1930 in the mass spectrum. The ^1H nmr spectrum when taken in deuterochloroform displayed clearly, in addition to three singlets at δ 1.14, 1.26 (C-13 and C-14 methyls) and 1.50 (C-12 methyl), a doublet at δ 1.00 and a doublet of doublet at δ 4.12 due to the C-15 methyl and C-6 proton respectively. By selective spin-spin decoupling, the chemical shifts of the three protons on C-4 (δ 2.31) C-5 (1.92) and C-7 (1.92) were confirmed. On the other hand the ^1H nmr spectrum when recorded in pyridine-d_5 exhibited three methyl singlets at δ 1.26, 1.33 (C-13 and C-14 methyl), and 1.88 (C-12), a C-15 methyl doublet at δ 1.07 and a doublet of doublets at δ 4.38 for the C-6 proton. The protons on C-4, C-5, and C-7 were shown to resonate at δ 2.80, 2.00 and 2.00 respectively again using spin-spin decoupling technique. An examination of Table I which summarizes these ^1H nmr spectral data reveals that

Table 1. Pyridine-induced Chemical Shifts (δ) in Alcohol 123



123

Proton	Pyridine-d_5	$CDCl_3$	$\Delta(\delta_{py}-\delta_{CDCl_3})$ (ppm)
C-4	2.80	2.31	0.49
C-5	2.00	1.92	0.08
C-6	4.38	4.1	0.28
C-7	2.00	1.92	0.08
C-15	1.07	1.00	0.07
C-12	1.88	1.50	0.38
C-13 or C-14	1.26 (1.33)*	1.14	0.12 (0.19)*
C-14 or C-13	1.33 (1.26)*	1.26	0.07 (0.00)*

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* The Figure in parenthesis indicates the possible alternative value.

when the solvent was changed from deuterochloroform to pyridine-d_5, the C-4 proton and the C-12 methyl experienced a large downfield shift of 0.49 and 0.38 respectively whereas the signals corresponding to protons on C-5, C-7 and C-15 remained virtually unchanged (< 0.08 ppm shift). The observed pyridine-induced chemical shifts required the ether bridge and the C-4 hydrogen atom be in close proximity to the hydroxy group and that the C-15 methyl and the C-5 and C-7 proton be distant from it (80) and thus the stereochemistry of 123 as depicted.

To complete the synthesis of a C-5 epimer of kessane (9) it required the removal of either the carbonyl from keto ether 121 or the hydroxy group from 123. The former possibility was first explored but proven to be fruitless. Reduction of 121 using Wolff-Kishner reaction and Clemmenson reduction resulted in recovery of the starting material. The same result was obtained when 121 was subjected to thioketalization with 1,2-ethanedithiol and boron trifluoride etherate under normal conditions when the more forceful conditions (higher concentration of the acid and higher temperature) were applied, a complex mixture was formed. The difficulties encountered were apparently due to the steric congestion of the ketone carbonyl as well as the instability of the ether linkage towards acid.

Alternatively, alcohol 123 was subjected to investigation for the removal of its hydroxy group. Toward this and, initial efforts were made to convert it into a mesylate or a halide both of which have been shown by Masamune et al. (81) to be easily reducible using metal hydride-copper(I) complexes. Treatment of 123 with methansulfonyl chloride in pyridine gave, instead of the corresponding mesylate, a mixture of dehydrokessane (80) and Δ^5-dehydrokessane (81) in 72% and 25% yield respectively as a result of dehydration (presumably via mesylate) and partial isomerization. The structures of these two products were evident from the following spectral data. The major isomer 80 showed, in the ^{1}H nmr spectrum, the C-15 methyl doublet at δ 1.03, a methyl singlet at 0.91 attributed to the C-12 methyl group which lies within the shielding zone of the double bond as revealed by Drieding model, a six-proton singlet for the remaining methyls, and the absence of signal for a vinylic proton. Although, a molecular ion peak was not observed in the mass spectrum, a base peak at m/e 205.1519 corresponding to the loss of a methyl group was in support of the structural assignment. In contrast to 80 the minor isomer 81 showed, in the ^{1}H nmr spectrum, a doublet at δ 5.66 for an olefinic proton. Three methyl singlets at δ 1.12, 1.18, 1.28 and a doublet at δ 1.03 for C-15 methyl group were also observed. In the mass spectrum, a molecular ion peak at 220.1824 was in full accord with the required molecular formula of $C_{15}H_{24}O$. Treatment of alcohol 123 with thionyl chloride in benzene in an attempt to prepare the corresponding chloride, also resulted in dehydration and, in this case, complete migration of the double bond to give a 69% of dehydrokessane (80). Although the anticipated products were not formed, the above reactions completed the synthesis of two hitherto unknown dehydro-derivatives of kessane (9). A third method which also effected the dehydration of 123 was the use of phosphoryl chloride in pyridine. This procedure was found to give also exclusively dehydrokessane (80) but in a slightly better yield of 73%.

It has been shown recently by Ireland and coworkers (82) that the replacement of a hydroxy group with a hydrogen atom could be effected by reacting the alcoholate anion with N,N,N',N'-tetramethyldiamidophosphorochloridate followed by treatment of the resulting N,N,N',N'-tetramethylphosphorodiamidate derivative with lithium-ethylamine. The possible use of this reductive deoxygenation method was investigated. Apparently due to the steric congestion of the hydroxyl group, 123 was found to be completely unreactive toward N,N,N',N'-tetramethyldiamidophosphorochloridate. Under both the reported and modified conditions, the starting material was recovered intact. Further studies using more reactive N,N-dimethylphosphoramidic dichloride (83) were, however, shown to be promising. In contrast to its lack of reactivity toward N,N,N',N'-tetramethyldiamidophosphorochloridate, the anion of 123 generated by n-butyllithium reacted smoothly with N,N-dimethylphosphoramidic dichloride in 1,2-dimethoxyethane and N,N,-N',N'-tetramethylethylenediamine at room temperature. The phosphorylation was found to be complete within 16 h. The resulting monochloride 124, which was shown by tlc to be the sole product, was conveniently converted to the desired N,N,N',N'-tetramethylphosphorodiamidate 125 by addition of dimethylamine prior to the work-up of the reaction.[9] The material was virtually free of impurities and a rapid column chromatography afforded a 95% yield of 125 which exhibited in the ^1H nmr spectrum, a doublet at δ 1.02 (C-15 methyl), three methyl singlets at δ 1.16, 1.28 (C-13 and C-14 methyls) and 1.50 (C-12 methyl), and a twelve-proton doublet at

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[9] This method has since been found to be general for the preparation of N,N,N',N'-tetramethylphosphorodiamidate derivatives of alcohols (84) and should prove especially useful for those alcohols in which the hydroxyl group is highly hindered.

2.66 for the four methyls on the nitrogen atoms. In the mass spectrum, a molecular ion peak appeared at 372.2545 as required.

Although the steric crowding of the hydroxyl group in 123 caused some initial difficulties for its conversion to *N*,*N*,*N*',*N*'-tetramethylphosphorodiamidate derivative and eventually lead to the development of the above procedure, the reductive cleavage of the C-O bond was uneffected by such a factor. Upon treatment with lithium in ethylamine, 125 underwent the reaction clearly to give a 79% yield of 5-epikessane (79). Although it was indistinguishable from natural kessane (9) in tlc, 5-epikessane (79) was found to be markedly different from 9 in spectral properties, particularly, the chemical shifts of the methyl groups in the ^{1}H nmr spectra. Their ^{13}C nmr[10], ir, ^{1}H nmr spectra are to be found in Fig. 1-7 for comparison.

In principle, following the reaction sequence described for its transformation to 5-epikessane (79),

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[10] It is noted that, in the ^{13}C nmr spectra, the C-15 carbon of epikessane (79) appeared at 23.1 ppm, whereas the corresponding carbon of kessane (9) was observed at a higher field at 18.6 ppm in agreement with the argumetn used for assigning *cis* stereochemistry to the ring junctures of several precursor of 79 (*vide supra*).

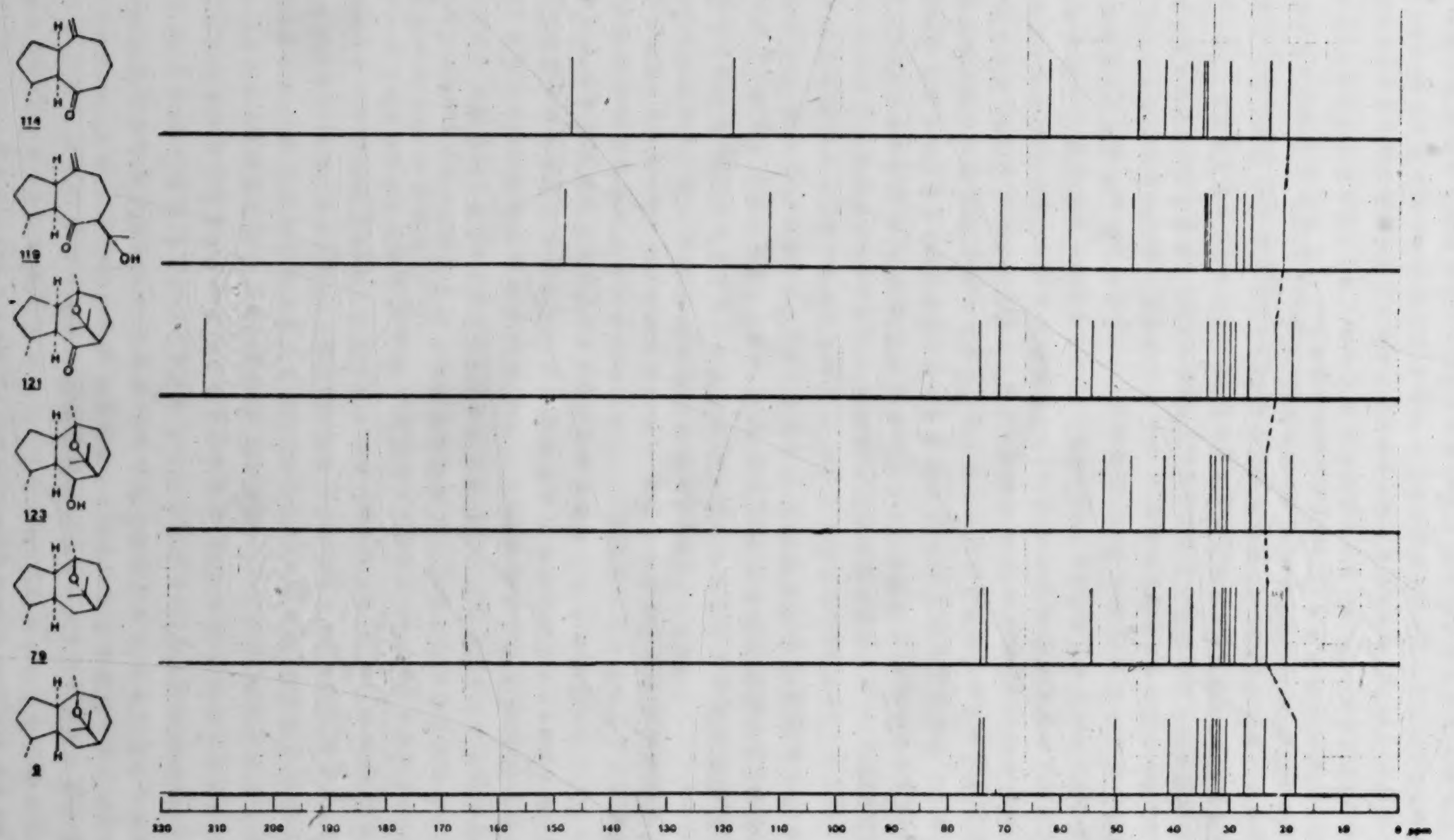


Fig. 1. Schematic representation of the ^{13}C spectra of 114, 119, 121, 123, 79, and 9. Higher positive numbers indicate decreased shielding. All values are reported from internal TMS.

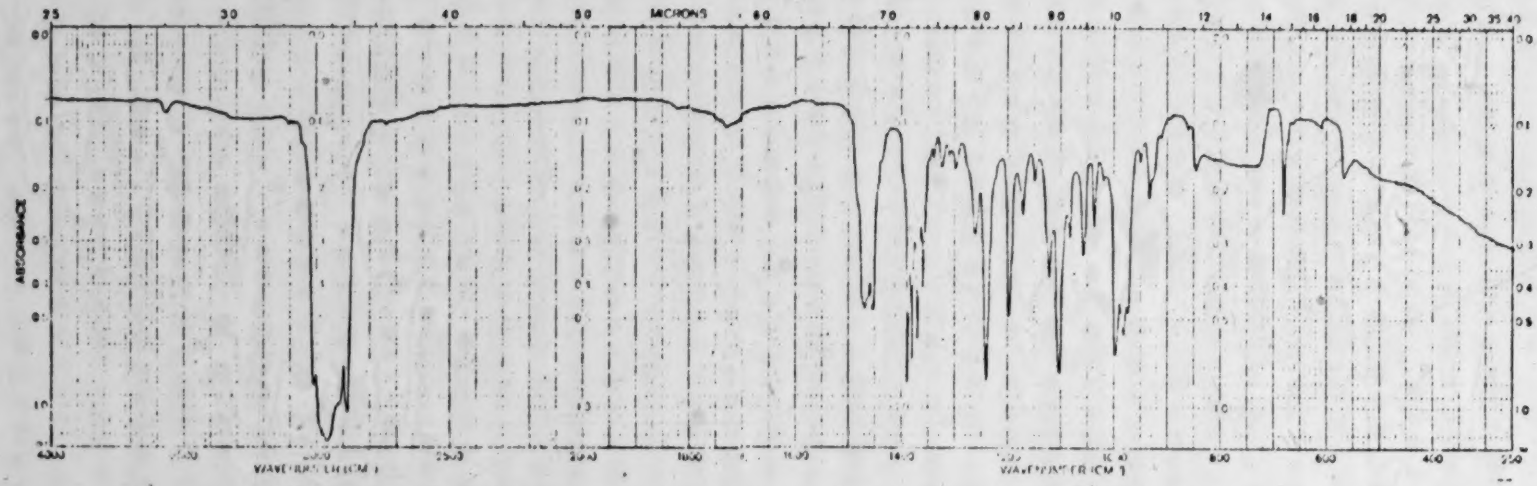


Fig. 2. Ir spectrum (CCl_4) of natural kessane (9).

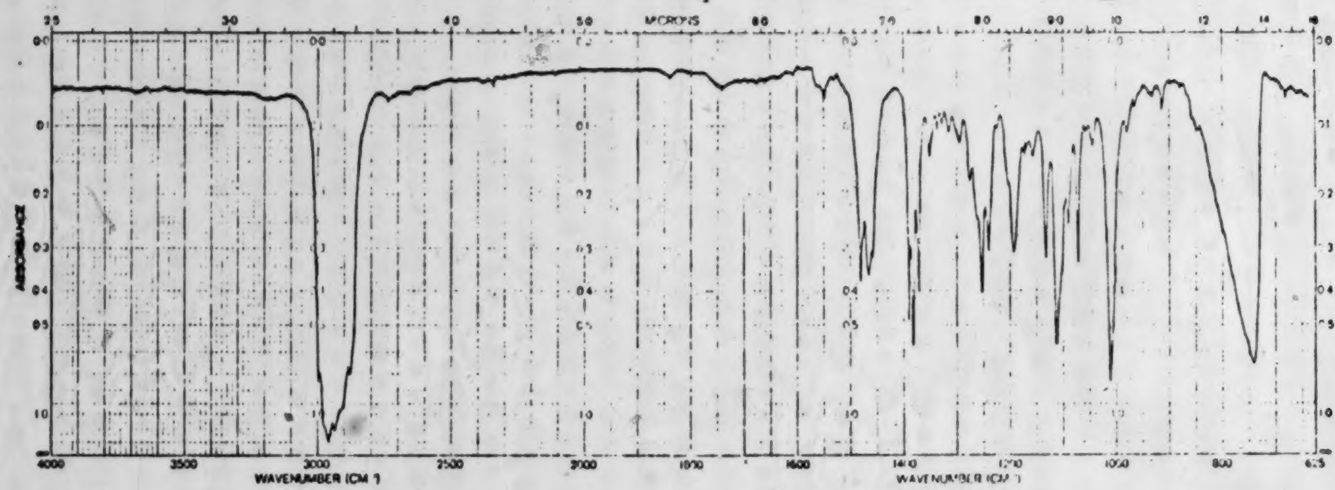


Fig. 3. Ir spectrum (CCl_4) of 5-epikessane (79).

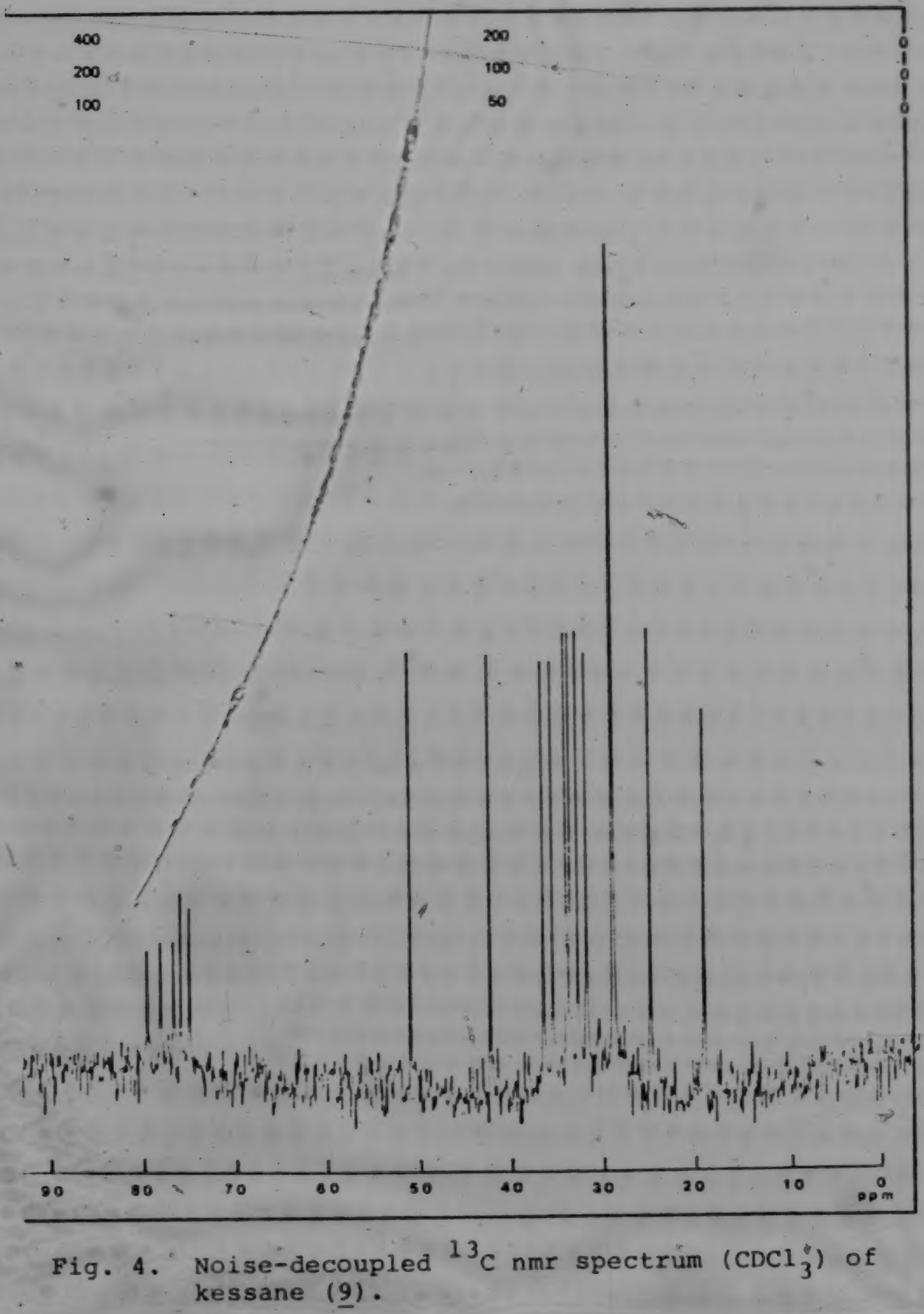


Fig. 4. Noise-decoupled ^{13}C nmr spectrum ($CDCl_3$) of kessane (9).

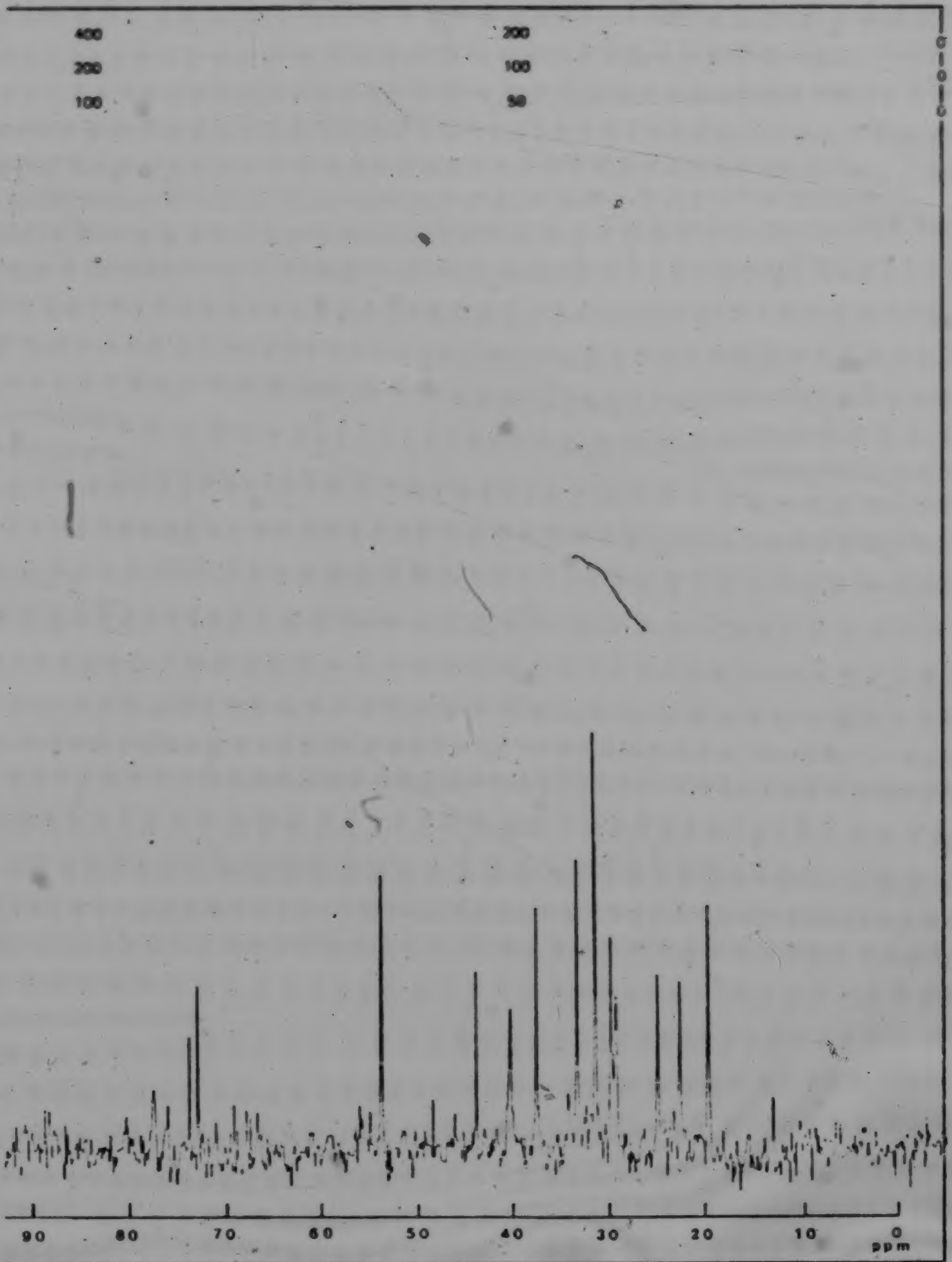


Fig. 5. Noise-decoupled ^{13}C nmr spectrum ($CDCl_3$) of 5-epikessane (79).

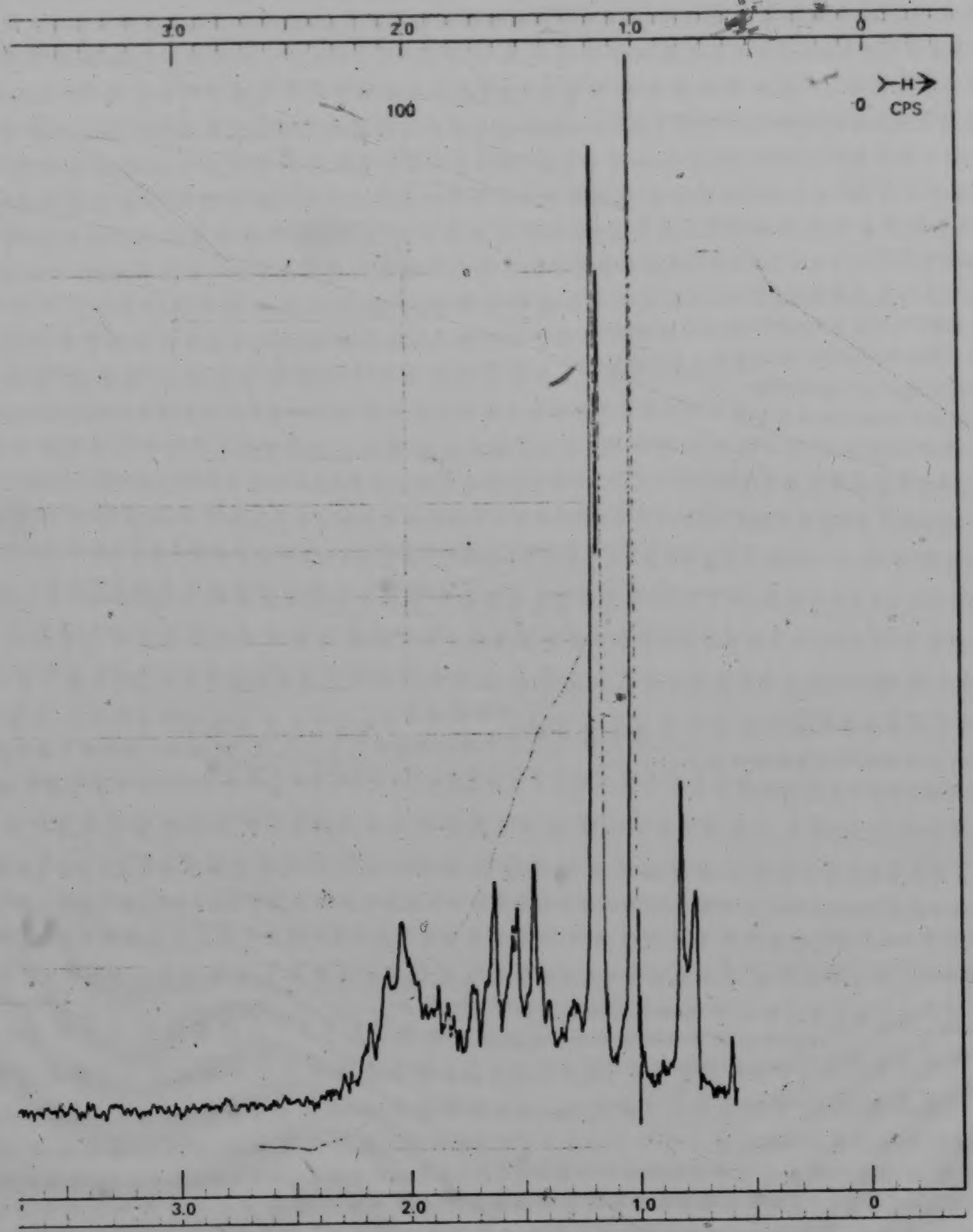


Fig. 6. ^1H nmr spectrum (CCl_4) of kessane (9).

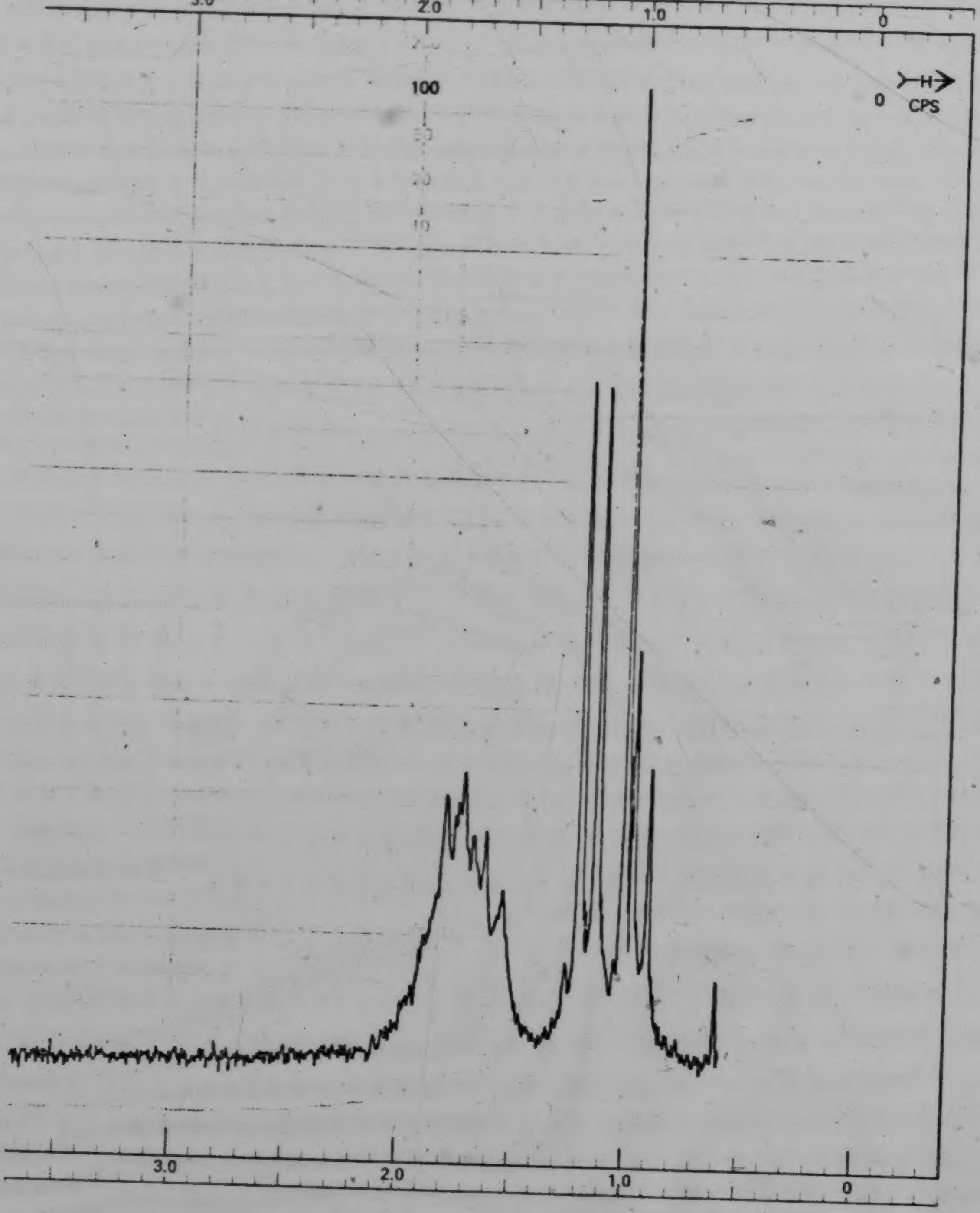
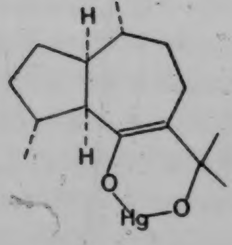


Fig. 7. ^{1}H nmr spectrum (CCl_4) of 5-epikessane (79).

ketone 121 could also be converted to the naturally occurring kessane (9) after epimerization at C-5. The following efforts made toward this direction, however, were not rewarding and the required epimerization has yet to be accomplished. Treatment of 121 with sodium methoxide in methanol at reflux for 24 h gave no detectable amount of the C-5 epimer of 121 but recovery of the starting material. To confirm that the conditions were sufficient for proton exchange, the reaction was repeated using methanol-d_1 as a solvent. The product thus obtained was mainly monodeuterated ketone 126 and the deuterium incorporation was shown to be approximately 98% by its mass spectrum. That the position of deuteration occurred specifically at C-5 was revealed by a comparison of its ^{1}H nmr with that of 121; the C-5 proton which appeared in the latter spectrum at δ 2.24 as a doublet of doublets was absent. These findings clearly indicated that 121 is by far more stable than its C-5 epimer and thus epimerization could not be achieved by a thermodynamically controlled process. Attempts epimerization using kinetic control proved to be equally unsuccessful, although a different kind of problem was involved. Treatment of 121 with a number of bases such as sodium amide, sodium hydride, sodium methoxide, lithium diisoproylamide in aprotic solvents under various condition failed to generate the required enolate ion as evident from the fact that quenching the reaction mixture with D_2O did not result in dueterium incorporation.

Since standard methods could not effect the epimerization, indirect chemical means were studied. The conversion of 121 to 9 could be realized by the introduction of a halogen atom (or alike) to C-5 followed by reductive cleavage of the carbon-halogen bond with stereochemical control after reducing or removing the ketone carbonyl (to prevent further epimerization at C-5). When ketone 121 was subjected to the treatment of pyridinium bromide perbromide in glacial acetic acid, it underwent bromination cleanly to give bromoketone 127 in 96% yield. A *cis* relationship between the bromine and the C-15 methyl was indicated by the ^1H nmr spectrum in which the latter group appeared at δ 1.37, a 0.32 ppm downfield shift from δ 1.05 observed for the corresponding group of the precursor, whereas other methyl signals remained virtually unchanged from those in ^1H nmr spectrum of 121. Subsequent reduction of 127 with lithium aluminum hydride afforded, instead of the desired bromohydrin 128, ketone 121 and alcohol 123 in 35% and 40% yield respectively. Interestingly, the isolation of 121 was shown to be independent of the length of reaction time or the amount of the reagent used. Accordingly, the ketone was not formed during the reaction and probably not responsible for the alcohol formation. As shown in Scheme X, a reasonable explanation could involve the debromination of 127 to generate an enolate ion which could either react immediately with the hydrogen bromide so generated to give ketone 121 which was further reduced to 123 or survive (part of the hydrogen bromide molecules formed were undoubtedly destroyed by lithium aluminum hydride) until the work-up to give 121. Should this proposal be valid, quenching the reaction mixture with deuterium oxide should lead to deuterated ketone 126 and no deuterium incorporation into the carbon atoms of 123. This turned out to be true and the ketone thus obtained had a deuterium incorporation of 73% by the mass spectrum. In addition to the understanding of the nature of the reaction, this experiment was particularly worthy for it provided an opportunity to determine whether the formation of 121 from its enolate ion was also favored by kinetical control. Other reducing agents were also used in attempts to convert 127 into 128. While sodium borohydride and diborane were found unreactive, the use of lithium borohydride and aluminum hydride afforded almost exclusively the alcohol 123.

The fact that 127 underwent reaction with reducing agents abnormally could be due to: (i) the large bromine atom poses addition shielding effect to the



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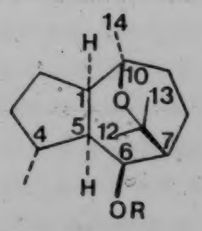
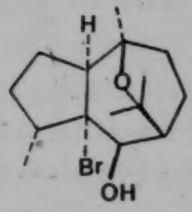


123: R = H

124: R = PO(Cl)N$(CH_3)_2$

125: R = PO$[N(CH_3)_2]_2$



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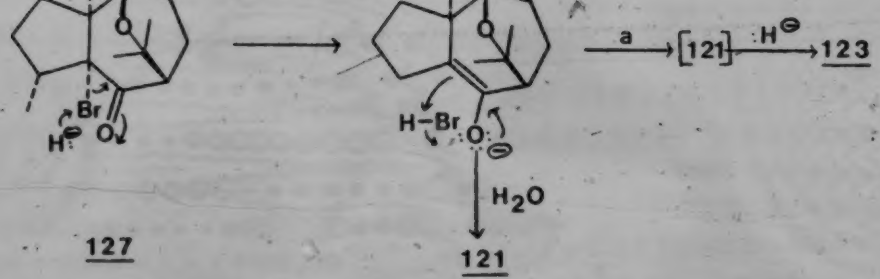


Scheme X

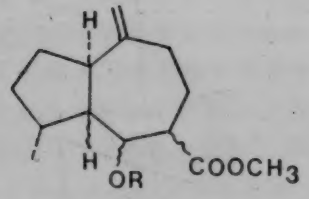
already sterically congested ketone carbonyl for its direct reduction and (ii) the C-Br bond is not strong enough to survive hydride attack. A remedy to these likely shortcomings could be the use of a smaller chlorine atom which also forms a stronger bond with carbon. Accordingly, ketone 121 was treated with sulfuryl chloride at room temperature, although slow (two days), the reaction gave a quantitative yield of the desired chloride 129. The orientation of the chlorine atom could be assigned again on the basis of the ^{1}H nmr spectrum. Disappointingly, the reduction of 129 using lithium aluminum hydride, lithium borohydride and aluminum hydride gave rise, without any exception to alcohol 123 in good yield.

As a consequence of the negative findings on the epimerization of 121, an alternative route possibly leading to kessane (9) was investigated using keto ester 118 as a starting point. It was felt that the observed stability of a cis ring juncture for all the hydroazulene derivatives so far obtained in this series might have been, in part, due to the relief of considerable steric strain between the methyl group on the five-membered ring and the oxygen atom of the ketone carbonyl. Under these considerations, it was desirable to remove the ketone carbonyl at the stage of 118 and to use its ester group to control (through a double bond) the stereochemistry at C-5. Thus, keto ester 118 was reduced with sodium borohydride at 0°C in methanol to give two inseparable diastereomers of hydroxy ester 130 whose ir spectrum displayed diagnostic absorption bands at 3510 cm^{-1} and 1730 cm^{-1} for the hydroxyl group and the ester carbonyl respectively. In the ^1H nmr spectrum, the proton neighboring to the hydroxyl group was found at δ 4.10 as a multiplet and the olefinic protons appeared at δ 4.83 and 4.84 as two singlets. Furthermore two methyl doublets at δ 1.04 and 1.06 as well as two singlets at δ 3.68 and 3.69 for the carbomethoxy group were indicative of the presence of two diastereomers. Acetylation of the hydroxy ester 130 with acetic anhydride in pyridine gave an 81% yield of the corresponding acetates 131. When 131 was heated with sodium hydride in 1,2-dimethoxyethane in the presence of a small amount of t-amyl alcohol at reflux for 16 h, the α,β-unsaturated ester 132 was obtained as a single isomer in 90% yield. The product showed, in the ir spectrum, an absorption band at 1710 cm^{-1} characteristic for the α,β-unsaturated ester carbonyl. In its ^1H nmr spectrum, a doublet due to the vinylic proton β to the ester appeared at δ 6.78 while a methyl doublet, a carbomethoxy singlet and a singlet for the remaining olefinic protons were found at δ 1.07, 3.70 and 4.72 respectively. The required molecular composition was confirmed by the mass spectrum showing a molecular ion peak at 220.1459. Although the structure of 131 could be readily deduced based from the spectral data, its stereochemistry at C-5 could not be assigned at this stage. The *cis* ring juncture was suggested by its subsequent transformation to 5-epikessane (79) under conditions unlikely to effect a complete epimerization at C-5. Subsequent reduction of 132 with lithium in liquid ammonia gave rise to a 37% yield of ester 133 whose ester carbonyl absorption appeared at 1735 cm^{-1} in the ir spectrum. In the ^1H nmr spectrum, the olefinic protons resonated at δ 4.70 as a singlet, while the carbomethoxy singlet and the methyl doublet appeared at δ 3.60 and 1.01 respectively. The same ester could also be prepared by a more efficient route described below.

Treatment of keto ester 118 with sodium hydride and chloromethyl methyl ether in hexamethylphosphoramide gave the corresponding enol ether 134 in 92% yield. It exhibited, in the ir spectrum, absorption bands at 1705 (α,β-unsaturated ester), 3090, 1640 and 900 cm^{-1} (double bonds). In addition to a methyl doublet at δ 1.13 and a carbomethoxy singlet at δ 3.62 the ^1H nmr spectrum showed two one-proton singlets for the olefin protons at δ 4.72 and 4.77 and two additional singlets at δ 3.37 and 4.70 attributed to the methyl and methylene protons of the enol ether unit. Although enol ether 134 of analytical purity could be obtained by a rapid column chromatography on alumina, the crude product was found to be sufficiently pure for the subsequent reduction with lithium-ammonia (85). The product thus obtained (41% yield from 118) was shown to be identical in all respects with ester 133.

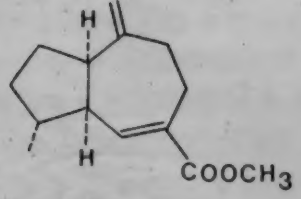
Treatment of 133 with excess methyllithium resulted in the formation of alcohol 135 in 90% yield. The ir spectrum of 135 exhibited, in addition to a strong absorption at 3610 cm^{-1} for the hydroxyl group, two characteristic bands at 1368 and 1380 cm^{-1} for the gem-dimethyl. In the ^{1}H nmr spectrum, a six-proton singlet appeared at δ 1.12 due to the gem-dimethyl. When alcohol 135 was subjected to oxymercuration (78) with mercuric acetate followed by sodium borohydride reduction of the resulting organomercury product, 5-epikessane (79) was formed in 71% yield. Although this route again failed to produce kessane (9), it simplefied the transformation of 118 to 5-epikessane (79) by one step and constitutes a second total synthesis of the latter compound involving a total of eleven steps.

In parallel to the above investigation, the possible extention of the 1,3-glycol cleavage reaction (109 → 114) to triol 136 was also studied. Not only would such an extension allow the preservation of a functionality



130:R = H

131:R = Ac



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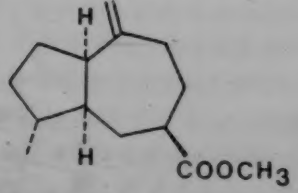

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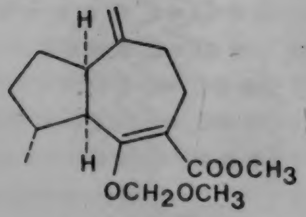

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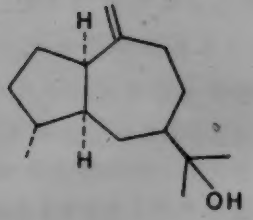
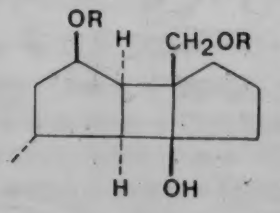
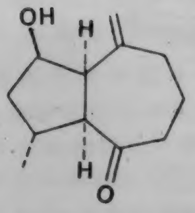


135



136: R = H

140: R = Ac



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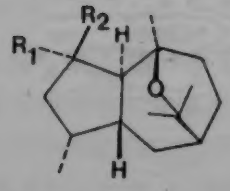
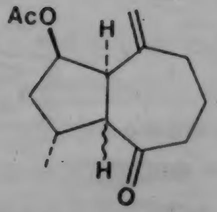


138: R_1 = H ; R_2 = OH

139: R_1, R_2 = O



141

in the five-membered ring and thus broaden the described method for hydroazulene synthesis, but the desired product 137 may find direct use in the synthesis of α-kessyl alcohol (138) and α-kessyl ketone (139) (86), two naturally occurring compounds closely related to kessane (9). Triol 136 (mp 1350-151°C) was readily prepared as a single isomer in 76% yield by lithium aluminum hydried reduction of ketone 88 (obtained in this case by desulfurization of 95 with mercuric chloride in aqueous acetonitrile). It showed, in ir spectrum, an intense hydroxy absorption band at 3400 cm^{-1} and, in the ^{1}H nmr spectrum, a methyl doublet at δ 0.87, two doublets integrated to one proton each at δ 3.24 and 3.91 for the two protons of the methylene bearing a hydroxy group, and a doublet of triplets at δ 4.32 for the methine proton neighbouring to the hydroxy. Treatment of 136 with p-toluenesulfonyl chloride in pyridine, under similar conditions which effected the 1,3-glycol cleavage of 109 to 114, gave a single product in 61% yield. Disappointingly, the product was found to be not the desired ketone 137, but a tetracyclic ether identical in all respects with 110. The exclusive participation of the secondary alcohol required its protection prior to the ring cleavage. Acetylation of triol 136 with acetic anhydride in pyridine afforded a diacetate 140 (mp 108-109°C) in 92% yield. The ir spectrum of 140 exhibited the characteristic absorption bands at 1730 cm^{-1} for the ester carbonyls and 3600, and 3500 cm^{-1} for the hydroxy group. In the ^{1}H nmr spectrum, a six-proton singlet attributed to the two acetoxy groups was found at δ 2.06 while the methine proton adjacent to the acetoxy group appeared as a doublet of triplet at δ 5.26 and two doublets at δ 4.28 and 4.46 were observed for the two protons of the acetoxymethylene. Although the use of an acetoxy moiety as a leaving group in Grobe-type fragmentation (73) was unprecedented, direct ring cleavage of 140 was attempted with the consideration that the high strain of the molecule might facilitate such a process even though the leaving group is poor. Indeed, when 140 was briefly treated with 3 equivalents of sodium hydride in dimethyl sulfoxide at room temperature, it underwent ring fission to give a 71% yield of keto acetate 141 which displayed in the ir spectrum, carbonyl bands at 1735 (ester) and 1710 cm^{-1} (ketone). In the ^{1}H nmr spectrum, the two olefinic protons resonated at δ 4.85 and 4.91 both as a doublet in agreement with the assigned structure. It was further confirmed by the mass spectrum showing a molecular ion peak at 236.1409. The stereochemistry of 141 at C-5, its possible use in the synthesis of kessyl alcohol (138) as well the transformation of ketone 121 to kessane (9) are the topics of continuing investigations.

EXPERIMENTAL

General

Melting points were determined on a Kofler hot stage apparatus and are uncorrected. Elemental analysis were performed by the microanalytic laboratory of this department. Ir spectra were recorded on a Perkin-Elmer Model 337 or 457 infrared spectrophotometer. ^1H nmr spectra were recorded on Varian A-60, HA-100, HA-100/Digilab and 90 MHz Perkin-Elmer 32 spectrometers, and ^{13}C nmr spectra on Bruker HFX-10/Nicolet 1085 spectrometer; using tetramethylsilane as an internal standard. The following abbreviation are used: s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet. Mass spectra were recorded using A.E.I. Model MS-2, MS-9 or MS-50 mass spectrometers. Gas chromatography (gc) was performed on a Hewlett Packed 5750 instrument using a stainless steel column (8' x 1/8") packed with 15% SE-30 on 80-100 mesh chromosorb W. Unless otherwise specified, anhydrous magnesium sulfate was used as drying agent for organic solutions and silica gel as adsorbant for column chromatography.

Materials

Ether, 1,2-dimethoxyethane (DME), tetrahydrahydrofuran (THF), and benzene used for reactions were freshly distilled from lithium aluminum hydride. Pyridine was dried over barium oxide and distilled. Dimethyl sulfoxide (DMSO) and hexamethylphosphoramide (HMPA) were distilled from calcium hydride. N,N,N',N'-Tetramethylethylidenediamine was distilled from molecular sodium. 2-Cyclopentenone was prepared from a mixture of 3,4- and 3,5-cyclopentenediol (Research Organic/Inorganic Chemical Corp) according to the known procedure (87). 2-Carbomethoxycyclopentenone was prepared by Dieckmann condensation of dimethyladipate which was obtained from adipic acid according to the reported procedure (88). Sodium hydride (50% dispersion in oil) was washed with n-pentane prior to use.

4-Acetoxy-2-cyclopentenone

The reported procedure (68) was used with modification. A mixture of 80 g (0.97 mol) of 2-cyclopentenone, 172 g (0.97 mol) of N-bromosuccinimide (NBS) and 3 g of α,α'-azodiisobutyronitrile in 1200 ml of carbon tetrachloride was heated at reflux for 1 h. The mixture was cooled to 0°C and filtered. The residue was washed thoroughly with ice-cold carbon tetrachloride. The filtrate after washing with ice-cold aqueous 1M sodium thiosulfate solution (2 x 300 ml), and water (300 ml), was dried over sodium sulfate, filtered and concentrated under reduced pressure (aspirator) to give 160 g of crude 4-bromo-2-cyclopenten-1-one. This oily product, without purification, was dissolved in 1000 ml of glacial acetic acid and silver acetate (159 g, 0.975 mol) was added. After heated at reflux for 24 h, the reaction mixture was filtered and the residue washed with glacial acetic acid. Removal of the solvent *in vacuo* followed by distillation of the remaining oil yielded 82 g (60%) of 4-acetoxy-2-cyclopenten-1-one as a colorless oil: bp 48°/0.3 torr; ir (film), 1743 (ester), 1730 (ketone) and 1593 (double bond); ^{1}H nmr (CCl_4) δ 2.14 (s, 3H, CH_3CO-) 2.25 (dd, 1H, J = 19, J' = 6 Hz, -C$\underline{\mathrm{H}}$(H)CO-), 2.71 (dd, 1H, J = 19, J = 3 Hz, -CH(H)CO-), 5.76 (dddd, 1H, J = 6, J' = 3, J" = 2, J‴ = 1 Hz, -$\overset{|}{\mathrm{C}}$HOCO-), 6.23 (dd, 1H, J = 6, J' = 1 Hz, -COCH=) and 7.52 (dd, 1H, J = 6, J' = 2 Hz, -C$\underline{\mathrm{H}}$=CHCO-); mass spectrum M^+ 140.0476 (Calcd. for $C_7H_8O_3$: 140.0474).

1-Acetoxy-2-carbomethoxycyclopentene (76)

To a solution of 2-carbomethoxycyclopentanone (706 g, 4.97 mol) in pyridine (789 g, 9.95 mol) at 0°C, was added dropwise acetyl chloride (585 g, 7.45 mol) over a period of one hour. The reaction mixture was stirred at room temperature under a nitrogen atmosphere for 24 h. After cooling to 0°C, ether (1000 ml) was introduced and the resulting mixture was acidified with ice-cold 10% H_2SO_4. The ether layer was separated and the aqueous solution extracted with ether (2 x 500 ml). The extracts were combined and washed successively with saturated aqueous sodium bicarbonate solution (200 ml) and brine (200 ml). Drying, filtration, and concentration of the extracts gave an oil (876 g) which was distilled at 57-58°/0.3 Torr to give 832.4 g (90%) of 76: ir (film) 1780 (enol acetate), 1725 (α,β-unsaturated ester) and 1665 cm^{-1} (double bond); ^1H nmr (CCl_4) δ 3.63 (s, 3H, $-COOCH_3$) and 2.30 (s, 3H, CH_3COO-).

7-Acetoxy-1-carbomethoxytricyclo[5.3.0.0^{2,6}]dec-4-ene-3-one (86a) and 1-Acetoxy-7-carbomethoxytricyclo-[5.3.0.0^{2,6}]dec-4-ene-3-one (87a and 87b)

In the photochemical reaction vessel (Fig. 8) were placed 15 g (0.107 mol) of 4-acetoxy-2-cyclopentenone, 300 g (1.87 mol) of 76 and 1000 ml of benzene. The reaction mixture was irradiated using a 450 W Hanovia high-pressure quartz mercury-vapor lamp and a Pyrex filter, at room temperature for 24 h. A constant flow of nitrogen was maintained to agitate the solution throughout the reaction period. Benzene was removed and excess 76 was recovered by distillation and recycled. After repeating the same process for three additional times using 20 g, 20 g, and 28 g of 4-acetoxy-2-cyclopentenone. A total amount of ~300 g of crude photoadduct was obtained. The crude product,

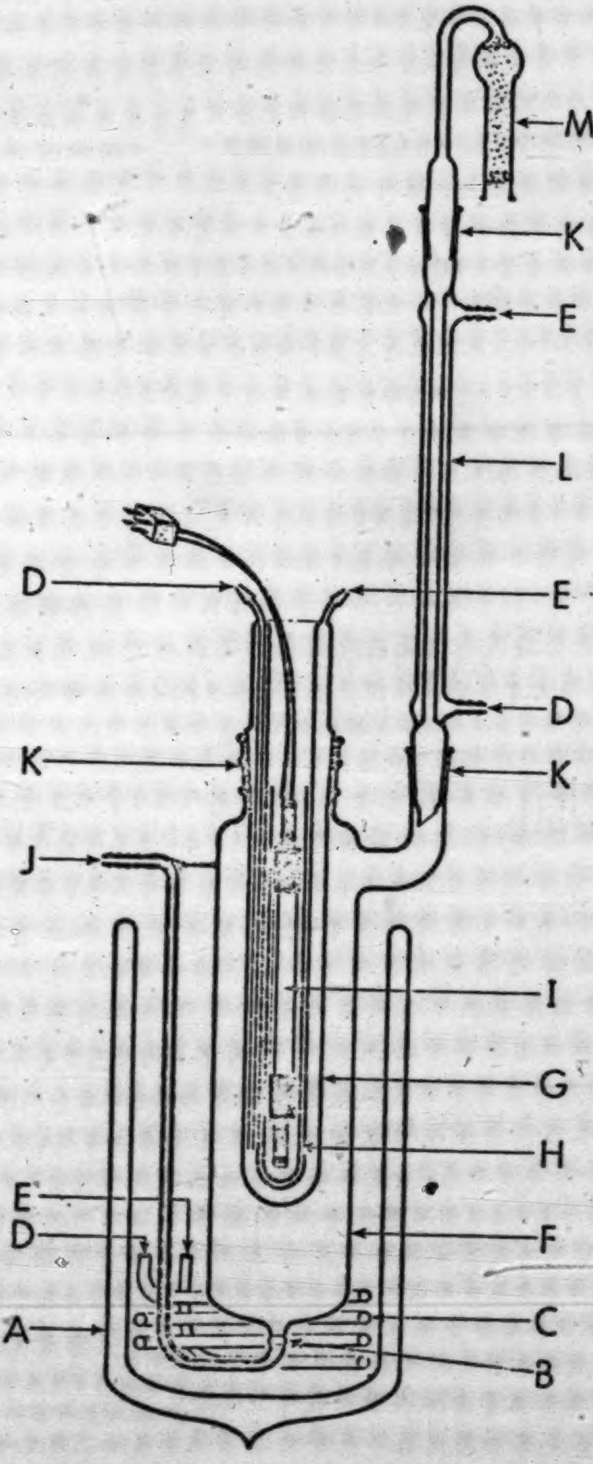


Fig. 8. A. Dewar flask; B. sintered glass filter; C. metal cooling coil; D. water inlet; E. water outlet; F. reaction vessel; G. quartz immersion well; H. pyrex filter; I. lamp; J. nitrogen gas inlet; K. ground glass joint; L. condenser; M. calcium chloride drying tube.

without purification was dissolved in 1000 ml of benzene and 30 g of p-toluenesulfonic acid was added. After stirring at room temperature for 48 h, the reaction mixture was washed with aqueous saturated sodium bicarbonate solution (2 x 150 ml) and water (2 x 100 ml), dried, filtered and concentrated to give 220 g of a viscous oil which was subjected to column chromatography. Elution with benzene gave 120 g (80%) of a mixture of 86a, 87a and 87b: ir (film) 1745 (ester), 1710 (α,β-unsaturated ketone), 1590 (double bond); ^{1}H nmr (CCl_4) δ 1.86, 1.92, 2.00 (all s, total 3H, CH_3COO-), 3.52, 3.56, 3.65 (all s, total 3H, $-COOCH_3$), 7.36, 7.78, 7.60 (all dd, total 1H, J = 5.3, J' = 1.2 Hz, -CH=CHCO-), 6.33, 6.30, 6.24 (all dd, total 1H, J = 5.3, J' = 0.6 Hz). Anal. Calcd.for $C_{14}H_{16}O_5$: C, 63.63; H, 6.09. Found: C, 63.63; H, 6.10.

A small amount of the mixture was further subjected to preparative high pressure liquid chromatography (Waters Associates Prep LC/System 500) using ether as eluent. This resulted in the isolation of 87a and the major stereoisomer of 86a in pure form. The later compound showed the following spectral data: ir (CCl_4) 1740 (ester), 1710 (α,β-unsaturated ketone), 1589 (double bond); ^{1}H nmr (CCl_4) δ 1.92 (s, 3H, CH_3COO-), 3.52 (s, 3H, $-COOCH_3$), 6.33 (dd, 1H, J = 5.3, J' = 0.6 Hz, =CHCO-), and 7.36 (dd, 1H, J = 5.3, J' = 1.2 Hz,

-CH=CHCO-). Anal. Calcd. for $C_{14}H_{16}O_5$: C, 63.63; H, 6.09. Found: C, 63.74; H, 6.16. The following physical properties was obtained for 87a: mp 103-104.5°C (ether); ir (CCl_4) 1740 (ester), 1710 (α,β-unsaturated ketone), 1589 (double bond); ^1H nmr (CCl_4) δ 1.86 (s, 3H, CH_3COO-), 3.56 (s, 3H, -$COOCH_3$), 6.24 (dd, 1H, J = 5.3, J' = 0.6 Hz, =CHCO-), 7.78 (dd, 1H, J = 5.3, J' = 1.2 Hz). Anal. Calcd. for $C_{14}H_{16}O_5$: C, 63.63; H, 6.09. Found: C, 63.29; H, 6.18.

7-Acetoxy-1-carbomethoxy-5-methyltricyclo[5.3.0.0^{2,6}]-decan-3-one (88) and 1-Acetoxy-7-carbomethoxy-5-methyl-tricyclo[5.3.0.0^{2,6}]decan-3-one (96) and (104)

(A) 88, 96 and 104 from a mixture of 86a, 87a and 87b.

At 0°C a solution of 3.00M methylmagnesium bromide in ether (140 ml, 0.42 mol) was added dropwise to a mixture of 40.6 g (0.218 mol) of cuprous iodide in ether (1000 ml). The resulting mixture was stirred for 10 min and a solution of 14 g (0.053 mol) of 86a, 87a and 87b in 200 ml of ether was added over a period of 10 min. After stirring for additional 30 min, the reaction mixture was poured into 1000 ml 4N aqueous ammonium hydroxide solution with vigorous stirring. The ether layer was separated and the aqueous solution extracted with ether (3 x 200 ml). The extracts were washed with brine, dried, filtered, and concentrated. Purification of the crude product by column chromatography using a solution of 5% ether in benzene as eluent gave 10.1 g (65%) of 88, 96 and 104 as a mixture: ir (CCl_4) 1745 (five membered ring ketone), and 1730 cm^{-1} (ester); ^1H nmr (CCl_4) δ 0.95, 1.07, 1.12 (all d, total 3H, J = 6.5 Hz, $\rangle CHC\underline{H}_3$), 1.98 (s, 3H, CH_3CO-), 3.59 and 3.66 (both s, total 3H, $-COOCH_3$); mass spectrum M^+ 280. Anal. Calcd. for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19. Found: C, 64.26; H, 7.16.

(B) 88 from 86a.

At 0°C, a solution of 86a (24 mg, 0.098 mmol) in 0.2 ml of ether, was added to a suspension of yellow methylmagnesium bromide-cuprous iodide complex in ether (prepared from 0.268 ml of a 2.92 M solution of methyl magnesium bromide in ether and 80.25 mg of cuprous iodide in 5 ml of ether according to the procedure described above). After stirring at 0°C for 20 min, the reaction mixture was poured into an ice-cold saturated ammonium chloride solution (25 ml) and extracted with ether (2 x 50 ml). Workup of the extracts in the usual manner afforded 20 mg of crude oil, which was purified by column chromatography. Elution with a solution of 2% ether in benzene gave 14 mg (56%) of 88: ir (CCl_4) 1745 cm^{-1} (ketone and ester); ^1H nmr (CCl_4) δ 1.07 (d, 3H, J = 6.5 Hz, $\rangle CHC\underline{H}_3$), 1.98 (s, 3H, CH_3COO-), and 3.60 (s, 3H,

-$COOCH_3$); mass spectrum M^+ 280.1310 (Calcd. for $C_{15}H_{20}O_5$; 280.1311). Anal. Calcd. for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19. Found: C, 64.37; H, 7.17.

(C) 96 from 87a.

Treatment of the minor isomer 87a (16 mg, 0.059 mmol) with methylmagnesium bromide-cuprous iodide complex using the same condition described above gave the corresponding isomer 96 (8.7 mg, 53%): ir (CCl_4) 1730-1750 cm^{-1} ester and cyclopentanone); ^1H nmr ($CDCl_3$) δ 0.97 (d, 3H, J = 6.5 Hz, $>CHC\underline{H}_3$); 1.98 (s, 3H, CH_3COO-), 3.56 (s, 3H, -$COOCH_3$); mass spectrum 280.1313 (Calcd. for $C_{15}H_{20}O_5$: 280.1311).

6-Carbomethoxy-10-methylbicyclo[5.3.0]decan-2,8-dione (90)

To a solution of 51 mg (0.18 mmol) of 88 in 1.5 ml of methanol was added 1.5 ml of 4N aqueous sodium hydroxide solution. The resulting solution was heated at reflux for 24 h under an atmosphere of nitrogen. After that time, it was cooled to 0°C and acidified with 2N HCl to ~pH 1. Extraction with chloroform followed by the usual workup of the organic solution gave 40 mg of acid 13: ir (CCl_4) 3490 (hydroxyl) 1745 (five membered ring ketone) and 1710 cm^{-1} (acid and seven membered ring ketones). The crude acid 89 without purification was esterified as follows. To a solution of crude acid 89 (40 mg) in acetone (2 ml) was added potassium carbonate (49.3 mg). The mixture was stirred at room temperature for 10 min and methyl iodide (0.1 ml) was introduced. Stirring was continued for 16 h. Water (10 ml) was added and the aqueous solution extracted with ether (2 x 50 ml). The organic solution was dried, filtered, and concentrated to afford 48 mg of solid. Recrystallization from ether-pentane yielded 31 mg (72%) of 90: mp 128-129°C; ir (CCl_4) 1740 (ester and five membered ring ketone) and 1710 cm^{-1} (seven membered ring ketone); ^1H nmr (CCl_4), δ 1.08 (d, 3H, J = 6.5 Hz, $>CHCH_3$) and 3.72 (s, 3H, $-COOCH_3$); mass spectrum M^+ 238.1212 (Calcd. for $C_{13}H_{18}O_4$: 238.1207); Anal. Calcd. for $C_{13}H_{18}O_4$: C, 65.52; H, 7.61. Found: C, 65.48; H, 7.71.

5-Acetoxy-3-methyl-11-oxatetracyclo[7.2.1.0.^{5,9}0^{4,12}]-dodecan-10-one (93) and 5-Acetoxy-3-methyl-11-oxatetracyclo[7.2.1.0.^{5,9}0^{4,12}]dodecan-10-one (94)

To a stirred solution of 88 (17 mg, 0.06 mol) in methanol (3 ml) at 0°C was added sodium borohydride (34 mg, 0.8 mmol). After 45 min, water (10 ml) was introduced and the resulting mixture extracted with ether (3 x 50 ml). The extracts were combined and worked up in the usual manner. On removal or the solvent, a mixture of two products was obtained. Column chromatography of the mixture using a solution of 5% ether in benzene as eluent gave 10.5 mg (67%) of crystalline 93: mp 135-136°C; ir (CCl_4) 1765 (γ-lactone) and 1738 cm^{-1} (ester); ^{1}H nmr (CCl_4) δ 1.05 (d, 3H, J = 6.5 Hz, $\rangle CHC\underline{H}_3$), 2.06 (s, 3H, CH_3COO-), and 4.97 (dd, 1H, J = 5, J' = 3 Hz, $-\overset{|}{C}\underline{H}O-$): mass spectrum m/e 208.1019 (m-42) (Calcd. for $C_{12}H_{16}O$: 208.1019. Anal. Calcd. for $C_{14}H_{18}O_3$: C, 67.18; H, 7.24. Found: C, 67.22; H, 7.17.

Further elution with ether-benzene (1:9) yield 4 mg (25%) of 94: mp 143-145°C; ir (CCl_4) 3600, 3450 (hydroxy), and 1735 cm^{-1} (ester); ^{1}H nmr (CCl_4) δ 1.00 (d, 3H, J = 6.5 Hz, $\rangle CHCH_3$), 2.04 (s, 3H, CH_3COO-), 4.80 (dd, 1H, J = 5, J' = 3 Hz, $-\overset{|}{C}HO-$), 5.40 (s, 1H, $O-\overset{|}{C}\underline{H}-O$). Anal. Calcd. for $C_{14}H_{20}O_3$: C, 66.72; H, 7.93. Found: C, 66.39; H, 7.84.

7-Acetoxy-1-carbomethoxy-3-ethylidenedithio-5-methyltricyclo[5.3.0.0^{2,6}]decane (95) 1-Acetoxy-7-carbomethoxy-3-ethylidenedithio-5-methyltricyclo[5.3.0.0^{2,6}]decane (97) and (105) 1-Carbomethoxy-1-(4-ethylidenedithio-2-methylcyclopentanyl)-2-ethylidenedithiocyclopentane (99) and 1-Carbomethoxy-1-(2-methyl-4-ethylidenedithiocyclopentanyl)-

2-cyclopentanone (98)

(A) 95 from 88.

To a solution of 88 (10 mg, 0.036 mmol) in 1 ml of 1,2 ethanedithiol, was added 0.1 ml of boron trifluoride etherate. After stirring at room temperature for 15 min, the reaction mixture was added to 25 ml ice-cold 4N aqueous sodium hydroxide solution and extracted with ether (2 x 50 ml). The extracts were washed with water (10 ml), dried, filtered and concentrated. The residue (15 mg) was chromotographed using a solution of 2% ether in benzene as eluent to give 10.6 mg (84%) of oily 95: ir (CCl_4) 1735 cm^{-1} (ester); ^1H nmr (CCl_4) δ 1.16 (d, 3H, J = 6.5 Hz, $>CHCH_3$), 1.99 (s, 3H, CH_3COO-), 3.20 (m, 4H, $-S(CH_2)_2S-$), and 3.57 (s, 3H, $-COOCH_3$); mass spectrum M^+ 356.1117 (Calcd. for $C_{17}H_{22}O_4{}^{32}S_2$: 356.1112). Anal. Calcd. for $C_{17}H_{22}O_4S_2$: C, 57.29; H, 7.05, S, 17.98. Found: C, 57.34; H, 6.85; S, 17.75.

(B) 97, 98 and 99 from 96.

To a solution of 96 (8.7 mg, 0.025 mmol) in 1 ml of 1,2 ethanedithiol, was added 0.1 ml of boron trifluoride etherate. After stirring at room temperature for 15 min , the reaction mixture was worked up in the usual manner to give a mixture (8 mg) of 97, 98 and 99.

(C) 95, 97, 99, 98 and 105 from a mixture of 88, 96 and 104.

To a solution of 10.2 g (0.036 mol) of the mixture of 5 and 6 in 100 ml of 1,2-ethanedithiol, was added 2 ml of boron trifluoride etherate. After stirring at room temperature for 20 min, the reaction mixture was poured into 700 ml of ice-cold 4N aqueous NaOH solution. The mixture was shaken vigorously and extracted with ether (3 x 1000 ml). The extracts were washed twice with 200 ml of brine, dried, filtered and concentrated to give 14.7 g of viscous oil which was subjected to column chromatography. Initial elution with benzene gave 2.4 g (16.8%) of 99: ir (CCl_4) 1725 cm^{-1} (ester); ^1H nmr δ 1.16 (d, 3H, J = 6.5 Hz, $>CHC\underline{H}_3$), 3.20 (s, 8H, $-SCH_2CH_2S-$), and 3.68 (s, 3H, $-COOCH_3$); mass spectrum M^+ 390.0805 (Calcd. for $C_{17}H_{26}O_2{}^{32}S_4$: 390.0816). Anal. Calcd. for $C_{17}H_{26}O_2{}^{32}S_4$: C, 52.29; H, 6.66; S, 32.84. Found: C, 52.51; H, 6.70; S, 32.56. Further elution with benzene yielded 1.51 g (13.0%) of 98: ir (CCl_4) 1725 (ester) and 1750 cm^{-1} (five membered ring ketone); ^1H nmr δ 0.93 (d, 3H, J = 6.5 Hz, $>CHC\underline{H}_3$), 3.20 (s, 4H, $-SCH_2CH_2S-$), 3.60 (s, 3H, $-COOCH_3$); mass spectrum 314.1002 (Calcd. for $C_{15}H_{22}O_3{}^{32}S_2$: 314.1011). Anal. Calcd. for $C_{15}H_{22}O_3{}^{32}S_2$: C, 57.28; H, 7.00; S, 20.39. Found: C, 57.45, H, 7.00; S, 20.70.

On further elution with a solution of 2% ether in benzene 100 mg 97 (~1%) was obtained. It showed the following spectral data: ir (CCl_4) 1735 cm^{-1} (ester); ^1H nmr (CCl_4) δ 1.19 (d, 3H, J = 6.5 Hz, $\rangle CH\underline{H}_3$), 1.98 (s, 3H, CH_3COO-), 3.14 (s, 4H, $-S-CH_2CH_2S-$), and 3.57 (s, 3H, $-COOCH_3$); mass spectrum M^+ 356.1122 (Calcd. for $C_{17}H_{24}O_4{}^{32}S_2$: 356.1117). Anal. Calcd. for $C_{17}H_{24}O_4S_2$: C, 57.29; H, 7.05; S, 17.98. Found: C, 57.26; H, 6.99; S, 17.62. Elution further with the same solvent system furnished a mixture of 97 and 95 (300 mg) *ca.* 1:1 ratio and pure 95 (6.1 g, 47%). Final elution with a solution of 5% ether in benzene afforded a *ca.* 1:1 mixture of 95 and 105 (600 mg). The ^1H nmr of this mixture showed in addition to signals corresponding to those of 10, peaks at δ 1.19 (d, 3H, J = 6.5 Hz, $\rangle CH\underline{H}_3$), 1.91 (s, 3H, CH_3COO-), 3.28 (s, 4H, $-S(CH_2)_2S-$), and 3.62 (s, 3H, $-COOCH_3$).

Conversion of 95 into 88.

A mixture of 113 mg (0.3 mmol) of 95, 0.344 g (1.2 mmol) of mercuric chloride in 4 ml of water-acetonitrile (1:3) was stirred at room temperature for 3 h. The mixture was filtered and the filtrate diluted with 50 ml of water. The aqueous solution was extracted with ether (3 x 100 ml). The extracts were combined, washed successively with saturated aqueous ammonium acetate solution (50 ml) and water (50 ml), dried, and filtered. Concentration of the filtrate gave an oily residue (100 mg) which was chromatographed. Elution with a solution of 5% ether in benzene furnished 71 mg (81%) of 88 identical in all respects with a sample obtained previously.

2-Carbomethoxy-2-(2-methyl-4-oxocyclopentanyl)-cyclopentanone (101)

A mixture of 135 mg (0.43 mmol) of 98, 240 mg (1.2 mmol) of mercuric chloride and 187 mg (0.6 mmol) of mercuric oxide in 10 ml of methanol-water (10:1) was stirred at room temperature for 24 h and refluxed for 1 hr. The reaction mixture was diluted with 10 ml of water and filtered. The filtrate was extracted with ether (3 x 10 ml) and the combined extracts washed successively with 20 ml each of saturated aqueous ammonium acetate and water. After the usual workup an oil (100 mg) was obtained which was column chromatographed with benzene elution to afford 61 mg (59%) of 101: ir (CCl_4) 1750 (ketone) and 1730 cm^{-1}(ester); ^1H nmr (CCl_4) δ 0.97 (d, 3H, J = 6.5 Hz, $>CHCH_3$) and 3.64 (s, 3H, $-COOCH_3$); mass spectrum M^+ 238.1209 (Calcd. for $C_{13}H_{18}O_4$: 238.1205).

5-Ethylidenedithio-7-hydroxymethyl-3-methyltricyclo-[5.3.0.0^{2,6}]decan-1-ol (106)

A mixture of 95 (723 mg, 2 mmol) and 193 mg (5 mmol) of lithium aluminum hydride in 60 ml of ether was heated at reflux under a nitrogen atmosphere for 30 min. The reaction mixture was cooled to 0°C and saturated sodium bicarbonate was added (25 ml). The mixture was filtered and the residue washed thoroughly with ether. The ether layer was separated and the aqueous portion extracted with ether (2 x 100 ml). The combined ether solution after the usual workup afforded 690 mg of an oil which was purified by column chromatography. Elution with a solution of 5% ether in benzene gave 401 mg (69%) of 106: ir (CCl_4) 3480 cm^{-1} (hydroxy). ^1H nmr (CCl_4) δ 1.22 (d, 3H, J = 6.5 Hz, $>CHC\underline{H}_3$), 3.12 (s, 4H, $-S(CH_2)_2S-$) and 3.70 (s, 2H, $-C\underline{H}_2OH$); mass spectrum m/e 286, 268 (m-18).

5-Hydroxy-3-methyl-11,14-dithiotetracyclo[7.5.1.0.^{5,9}0^{4,15}]-pentadec-1-ene (108)

A solution of 119 mg (0.41 mmol) of 106 and 81 mg (0.42 mmol) of p-toluenesulfonyl chloride in 10 ml of pyridine was stirred at room temperature under a nitrogen atmosphere for 24 h. The reaction mixture was poured into 50 ml of ice-cold 2N HCl and extracted with ether (3 x 100 ml). The extracts were washed with 5% aqueous sodium bicarbonate solution, water, dried, filtered and evaporated to dryness. The crude oil thus obtained was purified by column chromatography using benzene as eluent to give 62 mg (59%) of 108: ir (CCl_4) 3500 cm^{-1} (hydroxy); ^1H nmr ($CDCl_3$) δ 0.90 (d, 3H, J = 6.5 Hz. $>CHCH_3$), 2.70 (s, 2H, $-SCH_2-$), 2.85 (m, 4H, $-S(CH_2)_2S-$) and 5.78 (d, 1H, J = 3 Hz, -CH=); mass spectrum M^+ 286.

3-Methyl-6-oxatetracyclo[7.2.1.1.0.^{5,9}0^{4,12}]dodec-5-ol (110)

(A) From 106.

A mixture of 106 (230 mg, 0.825 mmol) and *ca.* 3 g of W-2 Ra-Ni[6] in 50 ml of 98% ethanol was refluxed for 16 h under an atmosphere of nitrogen. The resulting mixture was filtered and the residue was thoroughly extracted with ether. The filtrate was concentrated under reduced pressure (aspirator) to give 200 mg of an oil which was purified by column chromatography. On elution with a solution of 5% ether in benzene, 110 (122 mg, 76%) was obtained as a solid, mp. 71-72°C and showed the following spectral data: ir (CCl_4) 3480 (hydroxy), 1110 (ether); ^1H nmr ($CDCl_3$) δ, 0.96 (d, 3H, J = 6.5 Hz, $>CHCH_3$), 3.26, 3.67 (both d, 1H each, J = 10 Hz, $-OCH_2-$), and 4.25 (q, 1H, J = 3 Hz, $-O\overset{|}{C}H-$); mass spectrum M^+ 194.1301 (Calcd. for $C_{12}H_{18}O$: 194.1306).

(B) From 136.

To a solution of 46 mg (0.22 mmol) of 136 in 5 ml of pyridine, was added 49 mg (0.26 mmol) of p-toluenesulfonyl chloride. The reaction mixture, after standing at room temperature for 24 h under a nitrogen atmosphere was poured into 50 ml of ice-cold 2N hydrochloric acid and extracted with ether (3 x 100 ml). The extracts were washed successively with 5% aqueous sodium bicarbonate and water (25 ml each). Drying, filtration and concentration of the organic solution gave an oil (35 mg). Column chromatography of the crude product using a solution of 5% ether in benzene as eluent afforded 29 mg (61%) of 110.

1-Acetoxy-7-carbomethoxy-3-methyl[5.3.0.0$^{2.6}$]decane (111)

Thioketal 95 (5.00 g, 14 mmol) was dissolved in 500 ml of 98% ethanol and ca. 50 g of W-2 Ra-Ni^{6} was added. The mixture was heated at reflux for 18 h. Raney Nickel was filtered off and washed thoroughly with ether (1000 ml). After concentration of the filtrate, it gave 6 g of an oil which was subjected to column chromatography. Elution with n-pentane-benzene (1:1) afforded an 1:1 mixture (870 mg), ~30%) of 1,1'-(2'-methylcyclopentyl)-2-carbomethoxycyclopent-2-ene 112 and 1,1'(2'-methylcyclopentyl)-2-carbomethoxycyclopentane 113. The mixture showed the following spectral data: ir (CCl_4) 1735 (ester), 1710 (α,β-unsaturated ester) and 1628 $cm^{-}1$ (double bond): ^1H nmr (CCl_4) δ 0.91 (d, 3H, J = 6.5 Hz, $\rangle CHC\underline{H}_3$), 3.54 and 3.60 (both s, total 3H, $-COOCH_3$): mass spectrum m/e 208.1457 (Calcd. for $C_{13}H_{20}O_3$: 208.1464) and 210.1613 (Calcd for $C_{13}H_{22}O_3$; 210.1620). Further elution using benzene gave 2.31 g (62%) of 111: ir (CCl_4) 1735 cm^{-1} (ester); ^1H nmr (CCl_4) δ 0.92 (d, 3H, J = 6.5 Hz, $\rangle CHC\underline{H}_3$), 1.95 (s, 3H, CH_3CO-), and 3.54 (s, 3H, $-COOCH_3$); Anal. Calcd. for $C_{15}H_{22}O_4$: C, 67.64; H, 8.32. Found: C, 67.76; H, 8.26.

1-Hydroxy-7-hydroxymethyl-3-methyltricyclo(5.3.0.$0^{2,6}$]-decane (109)

At 0°C to a solution of 111 (1.89 g, 7.1 mmol) in 120 ml of THF, was added 674 mg (17.1 mmol) of lithium aluminum hydride. The reaction mixture was heated at reflux for 30 min under an atmosphere of nitrogen. After cooling to 0°C saturated aqueous sodium bicarbonate solution (25 ml) was slowly introduced. The mixture was filtered and the residue washed thoroughly with ether. The organic portion was separated and aqueous solution extracted with ether (3 x 50 ml). The organic solution was dried, filtered and concentrated. The white solid thus obtained was recrystallized form n-pentane-ether to give 1.35 g (95%) of 109: mp 86-87°C; ir ($CHCl_3$) 3500 cm^{-1} (hydroxy); ^1H nmr ($CDCl_3$) δ 0.86 (d, 3H, J = 6.5 Hz, $\rangle CHCH_3$), 3.44 (d, 1H, J = 11 Hz, -CH(H)OH) and 3.86 (d, 1H, J = 11 Hz), -CH(H)OH); mass spectrum m/e 178 (M—18). Anal. Calcd. for $C_{12}H_{20}O_2$: C, 73.43; H, 10.26, Found: C, 73.46; H, 10.14.

10-Methyl-6-methylidenebicyclo[5.3.0]decan-2-one (114)

Diol 109 (1.35 g, 6.88 mmol) was dissolved in 50 ml of pyridine and p-toluenesulfonyl chloride (2.02 g, 10.6 mmol) was added. After stirring at room temperature for 24 h under a nitrogen atmosphere, the reaction mixture was cooled to 0°C and acidified with ice-cold 2N HCl. The resulting solution was extracted with ether (3 x 150 ml) and the extracts washed successively with 1N HCl, dilute sudium bicarbonate solution, and saturated aqueous sodium chloride, dried, filtered and concentrated to give 1.30 g of an oil. Column chromatography using benzene as eluent gave 114 (1.02 g, 83%) as a solid: mp 32-34°C; ir (CCl_4) 1710 (ketone), 3090, 1645, 900 cm^{-1} (double bond); ^1H nmr (CCl_4) δ 0.96 (d, 3H, J = 6.5 Hz, $\rangle CHC\underline{H}_3$), 3.00 (dt, 1H, J = 7, J' = 5 Hz, $-CH_2C\underline{H}-CH$), 4.76 (d, 1H, J = 1 Hz, =CH(H)), and 4.80 (d, 1H, J = 1 Hz, =CH(H)); ^{13}C nmr ($CDCl_3$) ppm 19.8, 22.9, 30.2, 34.5, 34.8, 36.8, 42.0, 46.4, 62.2, 111.8, 148.5, and one carbon undetected. Anal. Calcd. for $C_{12}H_{18}O$: C, 80.85; H, 10.17. Found: C, 80.44; H, 9.88; mass spectrum m/e (% relative abundance) 178.1360 (M^+ 33.8) (Calcd. for $C_{12}H_{18}O$: 178.1358), 179.1360 (4.7).

7-Acetoxy-1-carbomethoxy-3-methyltricyclo[5.3.0.$0^{2,6}$]-decane (115)

To a solution of 97 (20 mg, 0.056 mmol) in 5 ml of 98% ethanol, was added ca. 200 mg W-2 Ra-Ni. After refluxing for 18 h, the mixture was cooled to room temperature, filtered and the filtered cake washed thoroughly with ether (200 ml). The filtrate was concentrated to give 17 mg of an oil. Column chromatography using benzene as eluent afforded 14 mg (94%) of 115: ir (CCl_4) 1738 cm^{-1} (esters); ^1H nmr δ 0.83 (d, 3H, J = 6.5 Hz, $>CHC\underline{H}_3$), 1.95 (s, 3H, CH_3CO-) and 3.56 (s, 3H, $-COOCH_3$); Anal. Calcd. for $C_{15}H_{22}O_4$: C, 67.64; H, 8.32. Found: C, 67.71; H, 8.21.

8-Methyl-6-methylidenebicyclo[5.3.0]decan-2-one (117)

A mixture of 115 (20 mg, 0.07 mmol) and lithium aluminum hydride (10 mg, 0.26 mmol) in 5 ml of tetrahydrofuran was heated at reflux for 30 min. After the usual workup, a crude crystalline diol 116 (15 g) was obtained: ir (CCl_4) 3600 cm^{-1}. Without further purification, it was dissolved in 4 ml of pyridine and *p*-toluenesulfonyl chloride (15 mg) was added and the resulting mixture stirred at room temperature for 16 h. The reaction mixture was worked up and the crude oil thus obtained was subjected to column chromatography purification to give 12 mg (90%) of crystalline 117: mp 33-34°C; ir (CCl_4) 3090 (double bond), 1695 (ketone), 1640, 900 cm^{-1} (double bond), ^1H nmr (CCl_4) δ 0.94 (d, 3H, J = 6.5 Hz, $\rangle CHC\underline{H}_3$), 3.16 (d x t, 1H, J = 7, J' = 5 Hz), 4.75, 4.86 (d, 1H each J = 1 Hz, $=C\underline{H}(H)$); mass spectrum M^+ 178.1362 (Calcd. for $C_{12}H_{18}O$: 178.1358); Anal. Calcd. for $C_{12}H_{18}O$: C, 80.85; H, 10.17. Found: C, 80.52; H, 10.21.

1-Hydroxy-d-7-hydroxy-d-methyl-3-methyltricyclo[$5.3.0.0^{2,6}$]decane (109a)

To a solution of 109 (35 mg, 0.18 mmol) in 3 ml of freshly distilled carbon tetrachloride, was added 0.3 ml of deuterium oxide. The mixture was stirred vigorously for 30 min. The organic solution was separated, dried, filtered and concentrated to give 33 mg (94%) of 109a: mp 32-34°C; mass spectrum m/e 178.1367 (M^+-20) (Calcd. for $C_{12}H_{18}O$: 178.1358). The ^1H nmr spectrum ($CDCl_3$) showed signals at δ 0.86 (d, 3H, J = 6.5 Hz, $-\overset{|}{C}HC\underline{H}_3$), 3.44 and 3.86 (both s, 1H each, J = 11 Hz, $-CH_2OD$) and a total of eighteen protons.

Fragmentation of 109a

A solution of 109a (33 mg, 0.16 mmol) and *p*-toluenesulfonyl chloride (35 mg, 0.16 mmol) in 2 ml of pyridine was stirred at room temperature for 16 h. After the solvent was removed under reduced pressure (0.5 Torr), a solid was obtained. Sublimation (80°C/0.5 Torr) of this material gave 26 mg (88%) of keto olefin 114, identical in all respects (ir, ^1H nmr and mass spectra) with that obtained previously from 20 (*vide supra*). Furthermore, in the mass spectrum the intensity of the m+1 peak was found to be 13.8% of that of the molecular ion peak at 178.1360 (Calcd. for $C_{12}H_{18}O$) indicating that deuterium incorporation, if any, was insignificant.

Attempted Epimerization of 114

To a solution of 114 (29 mg, 0.16 mmol) in 2 ml of methanol, was added sodium hydride (19 mg, 0.8 mmol). After refluxing for 24 h under a nitrogen atmosphere, the reaction mixture was cooled to 0°C and acidified with 2N HCl. Extraction with ether (3 x 50 ml), followed by the usual workup of the extracts gave 29 mg of a crystalline compound mp 32-34°C which was shown to be identical with the starting material by tlc and ir, ^{1}H nmr and ^{13}C nmr spectra.

3-Carbomethoxy-10-methyl-6-methylidenebicyclo[5.3.0]-decan-2-one (118)

At 0°C, to a solution of 114 (260 mg, 1.46 mmol) in 20 ml of DME was added 65 mg (2.8 mmol) of oil-free sodium hydride. After stirring at room temperature under a nitrogen atmosphere for 15 min, 2.5 ml of dimethylcarbonate was introduced. The resulting mixture was after refluxing for 18 h, cooled to 0°C, acidified with 3N HCl and extracted with ether (3 x 150 ml). The combined organic solution was dried and filtered. Concentration of the filtrate yielded 400 mg of an oil. Purification by column chromatography using a solution of 50% n-pentane in benzene gave 320 mg (93%) of 118: ir (CCl_4) 3450 (hydroxy) 3095 (double bond), 1745 (ester), 1710 (ketone), 1600 (enol double bond), 1645 and 900 cm^{-1} (double bond); ^{1}H nmr (CCl_4) δ 0.97, 1.05 (both d, total 3H, J = 6.5 Hz, $\rangle CHC\underline{H}_3$), 3.63, 3.64 (both s, total 3H, $-COOCH_3$), 4.74 and 4.85 (both s, 1H each, $=CH_2$); mass spectrum M^+ 236.1417 (Calcd. for $C_{14}H_{20}O_3$; 236.1413). Anal. Calcd. for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 70.86; H, 8.57.

3-[2(2-Hydroxypropyl)]-10-methyl-6-methylidenebicyclo[5.3.0]decan-2-one (119)

At 0°C, to a solution of 118 mg (0.49 mg) of 118 in 8 ml of THF under an atmosphere of nitrogen, was added oil-free sodium hydride (18 mg, 0.8 mmol). After stirring for 15 min, a 1.6M solution of methyllithium in ether (0.92 ml, 1.58 mmol) was added in one portion. Stirring was continued at room temperature for further 2 h. The reaction mixture was cooled to 0°C, acidified with 1N HCl, and extracted with ether (3 x 150 ml). The extracts were workup in the usual manner. The crude product thus obtained (120 mg) was subjected to column chromatography. Elution with a solution of 2% ether in benzene gave 65 mg (57%) of 119: ir (CCl_4) 3500 (hydroxy), 3100 (olefin), 1695 (ketone), 1645 and 900 cm^{-1} (olefin), 1365 and 1380 cm^{-1} (gem-dimethyl); ^1H nmr (CCl_4) δ 1.00 (d, 3H, J = 6.5 Hz, $>CHC\underline{H}_3$), 1.06, 1.11 (both s, 3H each, $-\overset{|}{C}(CH_3)_2$), and 4.80 (s, 2H, $=CH_2$); ^{13}C nmr ($CDCl_3$) ppm, 20.3, 26.9, 28.2, 29.3, 31.9, 33.5, 34.2, 34.3, 47.7, 59.0, 64.5, 71.6, 112.3, 149.5 and one carbon undetected. Mass spectrum M^+ 236.1771 (Calcd. for $C_{15}H_{24}O_2$: 236.1776). Anal. Calcd. for $C_{15}H_{24}O_2$: C, 76.22; H, 10.23. Found: C, 75.84; H, 10.32.

4,8,10,10-Tetramethyl-9-oxatricyclo$[6.2.2.0^{3,7}]$dodecan-2-one (121)

A mixture of 50 mg (0.21 mmol) of 119 and 100 mg (0.31 mmol) of mercuric acetate in 4 ml of aqueous THF (1:1) was stirred at room temperature for 20 min. To this reaction mixture were added 1 ml of 3N aqueous sodium hydroxide and 1 ml of 0.5M $NaBH_4$ in 3N aqueous NaOH. The mixture was then saturated with sodium chloride and 10 ml of ether was added. After filtration and dilution of the filtrate with 10 ml of water, the organic layer was separated and the aqueous portion extracted with ether (3 x 50 ml). The combined organic solution was worked up in the usual manner. Column chromatography of the oily product (50 mg) on neutral alumina (grade III) using n-pentane-benzene (3:2) as eluent gave 20 mg (61% based on consumed starting material) of 121 as a solid mp 41-42°C. Further elution with a solution of 40% n-pentane in benzene resulted in the recover of 17 mg of the starting material 119. Keto ester 27 showed the following spectral data: ir (CCl_4) 1705 (ketone), 1370, 1380 (gem-dimethyl) and 1095 cm^{-1} (ether); ^1H nmr ($CDCl_3$) δ 1.10 (s, 3H, $-O-\overset{|}{\underset{|}{C}}-CH_3$), 1.05 (d, 3H, J = 6.5 Hz, $\rangle CHC\underline{H}_3$), 1.21 (s, 3H, $-O-\overset{|}{\underset{|}{C}}-CH_3$), and 1.30 (s, 3H, $-O-\overset{|}{\underset{|}{C}}CH_3$); ^1H nmr (C_6D_6) δ 1.09 (d, 3H, J = 6.5 Hz, $\rangle CHC\underline{H}_3$), 1.10 (s, 3H, $-O-\overset{|}{\underset{|}{C}}-CH_3$), 1.11 (s, 3H, $O-\overset{|}{\underset{|}{C}}-CH_3$), 1.19 (s, 3H, $O-\overset{|}{\underset{|}{C}}CH_3$), 2.24 (dd, 1H, J = J' = 5 Hz, $-\underset{|}{C}HC\underline{H}\overset{|}{\underset{|}{C}}H-$), 2.30 (d, 1H, J = 5 Hz) unassigned 2.86 (septet, 1H, J = 4 Hz, $-\overset{|}{C}H-\overset{CH_3}{\underset{CH_2}{CH}}$); ^{13}C nmr ($CDCl_3$) ppm 18.2, 22.0, 27.4, 29.6, 30.0, 30.9 (2C), 32.4, 34.7, 51.8, 55.4, 57.2, 71.4, 74.0 and 213.90; mass spectrum, m/e (% relative abundance) 236.1774 (M^+, 48.7) (Calcd. for $C_{15}H_{24}O_2$: 236.1776), 237 (10.8). Anal. Calcd. for $C_{15}H_{24}O$: C, 76.22; H, 10.23. Found: C, 76.36; H, 10.32.

4,8,10,10-Tetramethyl-9-oxatricyclo[6.2.2.$0^{3,7}$]dodecan-2-ol (123)

To a solution of 121 (35 mg, 0.15 mmol) in 12 ml of THF at 0°C was added lithium aluminum hydride (11.2 mg, 0.3 mmol). The resulting mixture was heated at reflux for 30 min. After cooling to 0°C, the excess lithium aluminum hydride was destroyed by dropwise addition of saturated aqueous bicarbonate solution until evolution of hydrogen ceased. The mixture was filtered and the filtrate diluted with water and extracted with ether (3 x 75 ml). The combined organic solution was dried, filtered and concentrated to give an oil (38 mg) which was purified by column chromatography. Elution with benzene yielded 35 mg (99%)

of 123: ir ($\mathrm{CCl_4}$), 3630 (hydroxy), 1365, 1380 (gem-dimethyl) and 1100 $\mathrm{cm^{-1}}$ (ether); ^{1}H nmr δ 1.00 (d, 3H, J = 6.5 Hz, $>\mathrm{CHC\underline{H}_3}$), 1.14 (s, 3H, $-\mathrm{O}-\overset{|}{\underset{|}{\mathrm{C}}}\mathrm{CH_3}$), 1.26 (s, 3H, $-\mathrm{O}\overset{|}{\underset{|}{\mathrm{C}}}\mathrm{CH_3}$), 1.50 (s, 3H, $-\mathrm{O}\overset{|}{\underset{|}{\mathrm{C}}}\mathrm{CH_3}$), 2.31 (m, 1H, $\mathrm{CH_2\overset{|}{C}\underline{H}CH_3}$), and 4.12 (dd, 1H, J = J' = 5 Hz), $>\mathrm{C\underline{H}OH}$); ^{1}H nmr (pyridine-$d_5$) δ 1.07 (d, 3H, J = 6.5 Hz, $>\mathrm{CHCH_3}$), 1.26 (s, 3H, $-\mathrm{O}\overset{|}{\underset{|}{\mathrm{C}}}\mathrm{CH_3}$), 1.33 (s, 3H, $-\mathrm{O}\overset{|}{\underset{|}{\mathrm{C}}}\mathrm{CH_3}$), 1.88 (s, 3H, $-\mathrm{O}\overset{|}{\underset{|}{\mathrm{C}}}\mathrm{CH_3}$), 2.80 (m, 1H, $-\mathrm{CH_2\overset{|}{C}\underline{H}CH_3}$) and 4.38 (dd, 1H, J = J' = 5 Hz, $>\mathrm{C\underline{H}OH}$). ^{13}C nmr ($\mathrm{CDCl_3}$) ppm 18.8, 23.5, 26.0, 30.1, 30.7 (2C), 31.9, 32.3, 33.3, 42.7, 48.4, 53.7, 77.2, and two carbons undetected; mass spectrum $\mathrm{M^+}$ 238.1930 (Calcd. for $\mathrm{C_{15}H_{26}O}$: 238.1932).

Dehydrokessane (80) and Δ^5-Dehydrokessane (81)

(A) Using methanesulfonyl chloride.

To a solution of 123 (6 mg, 0.025 mmol) in 1 ml of pyridine was added 0.1 ml of freshly distilled methanesulfonyl chloride. After stirring at room temperature for 48 h under an atmosphere of nitrogen, the mixture was poured into ice-cold water (10 ml) and extracted with ether (3 x 75 ml). The combined organic solution was dried, filtered, and concentrated to give 6 mg of crude product which was purified by column chromatography. Elution with a solution of 40% n-pentane in benzene afford 4 mg (72%) of 80: ir ($\mathrm{CCl_4}$), 1100 $\mathrm{cm^{-1}}$ (ether) ^{1}H nmr ($\mathrm{CDCl_3}$) δ 0.91 (s, 3H, $-\mathrm{O}\overset{|}{\underset{|}{\mathrm{C}}}\mathrm{CH_3}$), 1.03 (d, 3H, J = 6.5 Hz, $\rangle\mathrm{CHC\underline{H}_3}$), 1.25 (s, 6H, $-\mathrm{O}\overset{|}{\underset{|}{\mathrm{C}}}\mathrm{CH_3}$); mass spectrum m/e 205.1590 (M-15) (Calcd. for $C_{14}H_{21}O$: 205.1591). Further elution using the same solvent system yielded 81 (1.4 mg, 25%) ^1H nmr ($CDCl_3$) δ 1.03 (d, 3H, J = 6.5 Hz, $\rangle\mathrm{CHC\underline{H}_3}$), 1.12 (s, 3H, $-\mathrm{O}\overset{|}{\underset{|}{\mathrm{C}}}\mathrm{CH_3}$), 1.18 (s, 3H, $-\mathrm{O}\overset{|}{\underset{|}{\mathrm{C}}}\mathrm{CH_3}$), 1.28 (s, 3H, $-\mathrm{O}\overset{|}{\underset{|}{\mathrm{C}}}\mathrm{CH_3}$) and 5.66 (d, 1H, J = 6 Hz, $=\mathrm{C\underline{H}}-$); mass spectrum M^+ 220.1824 (Calcd. for $C_{15}H_{24}O$; 220.1827.

(B) Using thionyl chloride.

A solution of 123 (5 mg, 0.02 mmol) and thionyl chloride (0.15 ml) in benzene (2 ml) was stirred at room temperature for 18 h. The mixture was added to 10 ml of water and extracted with ether (3 x 50 ml). The extracts were washed with 5% aqueous sodium bicarbonate (10 ml), and water. Drying, filtration and concentration gave 4 mg of an oil which was purified by column chromatography. Elution with n-pentane-benzene (2:3) yielded 3.2 mg (69%) of 80.

(C) Using phosphoryl chloride.

To a solution of 123 (10 mg, 0.047 mmol) in 1 ml of pyridine was added phosphoryl chloride (0.2 ml). After stirring at room temperature for 24 h and cooled to 0°C, the reaction mixture was diluted with ether (10 ml) and poured into ice-cold water (10 ml) and extracted with ether (3 x 75). The extracts were washed with 1N HCl (20 ml), water (10 ml), dried, filtered and concentrated to give an oil (11 mg) which was chromatographed. Elution with n-pentane-benzene afforded 6.6 mg (73%) of 80.

4,8,10,10-Tetramethyl-2[(*N*,*N*,*N*',*N*'-tetramethylphosphinyl)oxy]-9-oxatricyclo[6.2.2.$0^{3,7}$]dodecane (125)

To a stirred solution of 11 mg (0.04 mmol) of 123 in 4 ml of DME-TMEDA (4:1) was added a 2.38M solution of *n*-butyl lithium in ether (0.05 ml, 0.12 mmol). After stirring at room temperature for 10 min, 0.05 ml (0.42 mmol) of dimethylphosphoramidic dichloride (83) was introduced. The reaction mixture was stirred for 24 h and cooled to -78°C. Dimethylamine (1 ml) was introduced with the aid of a dry ice condenser and the resulting mixture was allowed to warm to 0°C. After stirring for additional 2 h at 0°C, the excess dimethylamine was evaporated by warming to room temperature, and water (10 ml) was added. Extraction with ether (3 x 50 ml) was followed by washing the extracts twice with water (25 ml each). Drying, filtration and concentration yielded 21 mg of an oil. Column chromatography using ether as eluent gave 15 mg (95%) of 125: ir (CCl_4) 1230 (P=O) and 990 cm^{-1} (P-O); ^1H nmr (CCl_4) δ 1.02 (d, 3H, J = 6.5 Hz, $>\mathrm{CHC}\underline{\mathrm{H}}_3$), 1.16 (s, 3H, $-\mathrm{O}\overset{|}{\underset{|}{\mathrm{C}}}\mathrm{CH_3}$), 1.28 (s, 3H, $-\mathrm{O}\overset{|}{\underset{|}{\mathrm{C}}}\mathrm{CH_3}$), 1.50 (s, 3H, $-\mathrm{O}\overset{|}{\underset{|}{\mathrm{C}}}\mathrm{CH_3}$), 2.66 (d, 12H, J = 10 Hz, $-N(CH_3)_2$) and 4.65 (m, 1H, $-\overset{|}{C}\underline{H}O$); mass spectrum M^+ 372.2545 (Calcd. for $C_{19}H_{37}N_2O_3P$: 372.2548).

5-Epikessane (79)

To a blue solution of lithium (28 mg, 4 x 10^{-3} g-atom) in 4 ml of anhydrous ethylamine at 0°C under an atmosphere of argon, was added dropwise a solution of 125 (15 mg, 0.4 mmol) in 20 ml of THF containing 0.2 µl of t-butyl alcohol. The reaction mixture, after stirring at 0°C for 20 min was quenched with 2 ml of water. Ether (10 ml) was added. The mixture was allowed to warm to room temperature, diluted with water (10 ml) and extracted with ether (3 x 50 ml). After the usual workup, the ethereal solution afforded a yellowish oil which was chromatographed with n-pentane-benzene (2:3) elution. 5-Epikessane 79 (6.6 mg, 71%) thus obtained showed the following spectral data: ir (CCl_4) 1110 (ether), 1370 and 1380 cm^{-1} (gem-dimethyl); ^1H nmr (CCl_4) δ 0.93 (d, 3H, J = 6.5 Hz, $>CHC\underline{H}_3$), 1.00 (s, 3H, $-O\overset{|}{\underset{|}{C}}CH_3$), 1.13 (s, 3H, $-O\overset{|}{\underset{|}{C}}CH_3$), and 1.20 (s, 3H, $-O\overset{|}{\underset{|}{C}}CH_3$); ^{13}C nmr ($CDCl_3$) ppm, 19.8, 23.1, 25.2, 29.7, 30.3, 31.8, 32.0 (2C), 33.8, 37.8, 40.5, 44.1, 54.0, 73.1, 74.0; mass spectrum M^+ 222.1983 (Calcd. for $C_{15}H_{26}O$: 222.1983).

Attempted Epimerization of 121

(A) Ketone 121 (27 mg, 0.1 mmol) was dissolved in methanol (3 ml) and sodium hydride (11 mg, 0.45 mmol) was added. The reaction mixture was heated at reflux under a nitrogen atmosphere for 24 h. After cooling in an ice bath, it was poured into water and extracted with ether (3 x 75 ml). Concentration of the dried extracts gave a ketone (25 mg) whose ir, ^1H nmr, ^{13}C nmr and mass spectra were identical to those of the starting material.

(B) Under the same condition, the reaction of 20 mg (0.085 mmol) of 121 and sodium hydride (8 mg, 0.34 mmol) in methanol-d_1 (89) gave after the workup (D_2O was used in place of H_2O), 20 mg of 126: ir (CCl_4) 2120 (C-D), 1705 (ketone), 1100 (ether, 1380 and 1370 cm^{-1} (gem-dimethyl); ^1H nmr (C_6D_6) δ 1.09 (d, 3H, J = 6.5 Hz, $\rangle CHC\underline{H}_3$), 1.10 (s, 3H, $-O-\overset{|}{\underset{|}{C}}CH_3$), 1.11 (s, 3H, $-O\overset{|}{\underset{|}{C}}CH_3$), 1.19 (s, 3H, $-O-\overset{|}{\underset{|}{C}}CH_3$), 2.30 (d, 1H, unassigned) and 2.86 (sextet, 1H, J = 5 Hz, $-CJ_2\overset{|}{C}\underline{H}CH_3$); mass spectrum m/e (% relative abundance), 236.1788 (m, 1.2) (Calcd. for $C_{15}H_{24}O$: 236.1786), 237.1852 (49.3) (Calcd. for $C_{15}H_{23}DO_2$: 237.1855), 239 (8). Deuterium incorporation calculated (90); 97.6% (singly labelled), 0% (doubly labelled).

3-Bromo-4,8,10,10-tetramethyl-9-oxatricyclo[$6.2.2.0^{3,7}$]-dodecan-2-one (127)

To a solution of ketone 121 (15 mg, 0.064 mmol) in glacial acetic acid (1 ml), was added pyridinium hydrobromide perbromide (30 mg, 0.072 mmol). The reaction mixture, after stirring at room temperature for 20 min was added to water (20 ml) and extracted with ether (3 x 75 ml). The extracts were washed successively with saturated aqueous sodium bicarbonate (25 ml) and water (20 ml). Evaporation of the dried extracts gave an oil (22 mg) which was purified by column chromatography. On elution with a solution of 25% benzene in n-pentane 127 (19.2 mg, 96%) was obtained. The product showed the following spectral data: ir (CCl_4) 1705 (ketone), 1100 (ether), 1370 and 1380 (gem-dimethyl); ^1H nmr (CCl_4) δ 1.10 (s, 3H, $-O\overset{|}{\underset{|}{C}}CH_3$), 1.19 (s, 3H, $-O\overset{|}{\underset{|}{C}}CH_3$), 1.34 (s, 3H, $-O\overset{|}{\underset{|}{C}}CH_3$) and 1.37 (d, 3H, $>CHCH_3$); mass spectrum m/e 235.1701 (M-79 and M-81) (Calcd. for $C_{15}H_{23}O_2$: 235.1768).

Reduction of 127 with Lithium Aluminum Hydride

(A) To a solution of 127 (13.3 mg, 0.041 mmol) in 2 ml of THF, at 0°C, was added lithium aluminum hydride (3.6 mg, 0.08 mmol). After stirring for 15 min saturated aqueous sodium bicarbonate solution (5 ml) was added and the resulting mixture filtered. The filtrate was added to water (10 ml) and extracted with ether (3 x 75 ml). The usual workup of the extracts was followed by column chromatography of the crude product. On elution with n-pentane-benzene (1:1) a colorless oil (3.5 mg, 35%) was obtained whose ir, ^{1}H nmr and mass spectra were found to be identical with those of 121. Further elution with benzene gave an alcohol (4 mg, 40%) identical with 123 in all respects.

(B) Under reaction condition similar to those above 127 (19.5 mg, 0.064 mmol) was reduced with lithium aluminum hydride. Prior to the workup of the reaction, an excess of deuterium oxide was added. Purification of the crude product by column chromatography gave 5.3 mg of the deuterated ketone 126 and 7.9 mg of the alcohol 123.

3-Chloro-4,8,10,10-tetramethyl-9-oxatricyclo[6.2.2.0^{3,7}]-dodecan-2-one (129)

To a solution of 121 (8 mg, 0.032 mmol) in 2 ml of carbon tetrachloride, was added sulfuryl chloride (0.2 ml). After stirring at room temperature for 2 days, the reaction mixture was added to water (15 ml) and extracted with ether (3 x 75 ml). The extracts were washed with saturated aqueous sodium bicarbonate

(25 ml), water (20 ml), dried, filtered and concentrated. The residue (12 mg) was column chromatographed using a solution of 25% benzene in n-pentane as eluent to give 9.1 mg (98%) of chloroketone 129: ir (CCl_4) 1705 (ketone), 1110 (ether), 1370 and 1380 cm^{-1} (gem-dimethyl); ^1H nmr (CCl_4) δ 1.11 (s, 3H, $-O\overset{|}{\underset{|}{C}}CH_3$), 1.21 (s, 3H, $-O\overset{|}{\underset{|}{C}}CH_3$), 1.34 (s, 3H, $-O\overset{|}{\underset{|}{C}}CH_3$) and 1.31 (d, 3H, J = 6.5 Hz, $\rangle CHC\underline{H}_3$); mass spectrum M^+ 270.1392 (Calcd. for $C_{15}H_{23}O^{35}Cl$: 270.1387).

Reduction of 129 with Lithium Aluminum Hydride

A mixture of 129 (5.7 mg, 0.021 mmol) and lithium aluminum hydride (3 mg, 0.07 mmol) in 2 ml of ether was stirred at 0°C for 15 min. Saturated aqueous sodium bicarbonate solution (5 ml) was added to the mixture and filtered. The filtrate was diluted with water (10 ml) and extracted with ether (3 x 75 ml). After the usual workup and purification of the crude product, an alcohol (4.2 mg, 84%) was obtained which was found to be identical in all respects with 123 obtained previously.

Reduction with Aluminum Hydride (90)

(A) Of 127.

To a solution of 127 (10 mg, 0.026 mmol) in 2 ml of ether at 0°C was added aluminum hydride (3.12 mg, 0.1 mmol). After stirring for 60 min, saturated aqueous sodium bicarbonate solution (10 ml) was added. The mixture was filtered and residue washed with ether. The ether portion was separated and the aqueous solution extracted with ether (3 x 50 ml). The combined organic solution was worked up in the usual manner. Purification of the crude product by chromatography using n-pentane-benzene (1:1) as eluent gave an alcohol (6 mg, 80%) identical in all respects with 123.

(B) Of 129.

Under reaction condition similar to these above, 129 (8 mg, 0.029 mmol) was reduced with aluminum hydride. After the usual workup and purification by column chromatography it gave an alcohol identical to 123.

2-Carbomethoxy-10-methyl-6-methylidenebicyclo[5.3.0]-decane-1-ol (130)

2-Acetoxy-3-carbomethoxy-6-methylidenebicyclo[5.3.0]-decane (131)

To a solution of 18 mg (0.076 mmol) of 118 in 2 ml of methanol at 0°C was added sodium borohydride (18 mg, 0.4 mmol). After stirring for 30 min, the reaction mixture was poured into water and extracted with ether (3 x 50 ml). Evaporation of the dried extracts gave 18 mg (99%) of a diasteromeric mixture 130: ir (CCl_4) 3510 (hydroxy), 3100 (olefin), 1730 (ester) and 900 cm^{-1} (olefin); ^{1}H nmr (CCl_4) δ 1.04, 1.06 (both d, total 3H, J = 6.5 Hz, $>CHC\underline{H}_3$), 3.68, 3.69 both s, total 3H, $-COOCH_3$), 4.10 (m, 1H, $-C\underline{H}OH$), 4.83 and 4.84 (both s, total 2H, $=CH_2$). This mixture was found to be homogeneous on t.l.c. and used directly in the following transformation. A mixture of crude 130 (18 mg) and 0.1 ml of acetic anhydride in 2 ml of pyridine was stirred at room temperature for 3 days under a nitrogen atmosphere. After cooling to 0°C, it was transferred into a separatory funnel containing 2N hydrochloric acid (25 ml) and 100 ml of ether. The ether layer was separated and the aqueous portion further extracted with ether (2 x 75 ml). The extracts were washed with 20 ml of 2N HCl and 10 ml of water, dried, filtered and concentrated. Column chromatography of the residue using a solution of 40% benzene in n-pentane as eluent gave 17.2 mg (81%) of 131 as a mixture of two diastereomers: ir (CCl_4) 3100 (olefin), 1740 (esters), 1640 and 900 cm^{-1} (olefin); ^{1}H nmr (CCl_4) δ 1.08, 1.09 (d, total 3H, J = 6.5 Hz, $>CHC\underline{H}_3$), 1.90, 1.94 (both s, total 3H, CH_3COO-), 3.60, 3.63 (both s, total 3H, $-COOCH_3$), 4.70 (s, 2H, $=CH_2$), and 5.10 (m, 1H, $-\overset{|}{C}\underline{H}-OAc$); mass spectrum M$^+$ 280.1676 (Calcd for $C_{16}H_{24}O_4$: 280.1674).

3-Carbomethoxy-10-methyl-6-methylidenebicyclo[5.3.0]-dec-2-ene (132)

To a solution of 131 (14 mg, 0.05 mmol) in 3 ml of DME containing 30 µl of *t*-amyl alcohol, was added sodium hydride (8 mg, 0.3 mmol). The resulting mixture was stirred at room temperature for 16 h under an atmosphere of argon. After cooling to 0°C, ether (20 ml) and water (10 ml) was added to the mixture. The organic layer was separated and the aqueous portion extracted with ether (3 x 75 ml). After the normal workup, the residue (14 mg) was chromatographed with *n*-pentane-benzene (1:1) elution to give 10 mg (90%) of 132: ir (CCl_4) 3090 (olefin), 1710 (α,β-unsaturated ester), 1635 and 900 cm^{-1} (double bond), 1600 cm^{-1} (α,β-unsaturated olefin); ^1H nmr (CCl_4) δ 1.07 (d, 3H, J = 6.5 Hz, $>CHC\underline{H}_3$), 3.70 (s, 3H, $-COOCH_3$), 4.72 (s, 2H, $=CH_2$), and 6.78 (d, 1H, J = 4 Hz, $-C\underline{H}=$); mass spectrum M^+ 220.1459 (Calcd. for $C_{14}H_{20}O$: 220.1463).

3-Carbomethoxy-10-methyl-6-methylidenebicyclo[5.3.0]-decane (133)

At -78°C, to a blue solution of lithium (15.7 mg, 0.0025 g-atom) in liquid ammonia (2 ml) under an argon atmosphere, was added a solution of 10 mg (0.045 mmol) of 132 in 0.2 ml of ether. The reaction mixture was refluxed (Dry ice-acetone condenser) for 10 min and solid ammonium chloride (1 g) added followed by 20 ml of ether. After warming to room temperature, the mixture was filtered. Concentration of the filtrate gave 6 mg of a viscous oil. Purification by column chromatography using a solution of 25% n-pentane in benzene as eluent gave 3.9 mg (37%) of 133: ir (CCl_4) 3090 (olefin), 1735 (ester, 1635 and 900 cm^{-1} (olefin); ^1H nmr (CCl_4) δ 1.01 (d, 3H, J = 6.5 Hz, $CHC\underline{H}_3$), 3.60 (s, 3H, $-COOCH_3$), 4.70 (m, 2H, $=CH_2$); mass spectrum M^+ 222.1624 (Calcd. for $C_{14}H_{22}O_2$: 222.1620). Further elutions with n-pentane-benzene (3:7) gave a mixture whose ir showed the absence of ester carbonyl absorption and a intense hydroxy absorption band at 3500 cm^{-1}.

3-Carbomethoxy-10-methyl-6-methylidene-2-(methoxymethoxy)bicyclo[5.3.0]dec-2-ene (134)

To a solution of 111 mg (0.47 mmol) of 118 in 4 ml of HMPA, was added 12 mg (0.5 mmol) of sodium hydride. The mixture was stirred at room temperature under a nitrogen atmosphere for 1 h. After cooling to 0°C, chloromethyl methyl ether (60 µl, 0.56 mmol) was added. The resulting mixture was warmed to room temperature and stirred for 2 h. After that time, it was poured into ice-cold saturated aqueous sodium bicarbonate solution (25 ml) and extracted with ether (3 x 100 ml). The extracts were washed with ice-cold water, dried, filtered and concentrated. The enol ether 134 (121 mg, 92%) thus obtained after column chromatography on neutral alumina showed the following spectral data: ir (CCl_4) 3090 (olefin), 1710 (α,β-unsaturated ester), 1640, 900 (olefin) and 1600 cm^{-1} (enol ether double bond); ^1H nmr (CCl_4) δ 1.13 (d, 3H, J = 6.5 Hz, $>CHC\underline{H}_3$), 3.37 (s, 3H, $-OCH_3$), 3.62 (s, 3H, $-COOCH_3$), 4.70 (s, 2H, $-OC\underline{H}_2O-$), 4.72 and 4.77 (both s, 1H each, $=CH_2$); mass spectrum M^+ 280.1678 (Calcd. for $C_{16}H_{24}P_4$: 280.1675). In the subsequent reaction, the crude material homogeneous on t.l.c. was used without further purification.

Reduction of 134

At -78°C (Dry ice-acetone bath), lithium (13 mg, 1.85×10^{-3} g-atom) was added to 5 ml of anhydrous ammonia. The mixture was stirred under an atmosphere of argon until all lithium metal dissolved. A solution of 63.6 mg (0.21 mmol) of 134 in 2 ml of ether was added. The Dry ice-acetone bath was removed and the reaction mixture was allowed to reflux (Dry ice-acetone condenser) for 15 min. After that period, it was cooled to -78°C and ammonium chloride (2 g) was added in one portion and followed by the addition of ether (20 ml).

After warming to room temperature, the solid ammonium chloride was filtered off and washed thoroughly with ether (100 ml). After concentration of the ether solution, a yellowish viscous oil (59 mg) was obtained. Purification by column chromatography with *n*-pentane-benzene (2:3) elution gave 21 mg (41%) of an ester identical in all respects with 133 obtained previously.

10-Methyl-6-methylidene-3-[2-(2-hydroxypropanyl)]-bicyclo[5.3.0]decane (135)

To a solution of 133 (30 mg, 0.135 mmol) in 4 ml of ether at 0°C, was added 0.3 ml (0.6 mmol) of a solution of 2.02M methyl lithium in ether. After stirring at room temperature under a nitrogen atmosphere for 3 h the reaction mixture was cooled to 0°C, and diluted with 10 ml of ether followed by the addition of water and 2N hydrochloric acid (3 ml each). The ether layer was separated, and the aqueous portion extracted twice with ether (20 ml each). The extracts were dried, filtered. Concentration of the filtrate and purification of the crude product by column chromatography with benzene elution gave 27 mg (90%) of 135: ir (CCl_4) 3610 (hydroxy), 3090, 1640, 890 (olefin), 1368 and 1380 cm^{-1} (gem-dimethyl); ^1H nmr (CCl_4) δ 0.96 (d, 3H, J = 6.5 Hz, $>CHC\underline{H}_3$), 1.12 (s, 6H, $-\overset{|}{C}(CH_3)_2$) and 4.64 (s, 2H, $=C\underline{H}_2$); mass spectrum m/e

204.1874 (M-18) (Calcd. for $C_{15}H_{24}$: 204.1878).

Cyclization of (135) to 5-Epikessane (79)

A mixture of 135 (4.5 mg, 0.02 mmol) and triflurомercuric acetate (18 mg, 0.027 mmol) in 1 ml each of water and THF was stirred at room temperature under a nitrogen atmosphere for 15 min. After which time, 3N aqueous NaOH (1 ml) and 0.5M $NaBH_4$ (in 3N NaOH; 1 ml) were added. After saturation with sodium chloride and filtration, the mixture was diluted with water (10 ml) and extracted with ether (3 x 75 ml). The organic solution after usual workup gave an oil which was purified by column chromatography. On elution with a solution of 75% n-pentane in benzene, 79 (2 mg, 71% based on the consumed starting material) was obtained. Further elution with n-pentane-benzene (1:1) resulted in the recovery of 1.7 mg of the starting alcohol 135.

7-Hydroxymethyl-3-methyltricyclo[5.3.0.$0^{2,6}$]decane-1,5-diol (136)

A mixture of 52 mg (0.185 mmol) of 88, 25 mg (0.66 mmol) of lithium aluminum hydride in 5 ml of THF, was heated at reflux for 90 min. After cooling to 0°C, a solution of saturated aqueous sodium bicarbonate (25 ml) was introduc d dropwise. The resulting mixture was filtered and filtered cake washed thoroughly with ether. The rganic layer was separated and aqueous solution ext acted with ether (3 x 150 ml). Evaporation of the driec ether solution gave an oily residue (40 mg) which was pu ified by column chromatography using a solution of 5% ether in benzene as eluent. The crystalline 136 30 mg, 76%), mp 150-151°C, thus obtained showed the f llowing spectral properties: ir (KBr) 3400 (hydro); ^{1}H nmr (DMSO-d$_6$) δ, 0.87 (d, 3H, J = 6.5 Hz, $>$CH $_3$), 3.24, 3.91 (both d, 1H, J = 12 Hz, -$\underline{\mathrm{CH}}_2$OH) and .32 (dt, 1H, J = 10, J' = 6 Hz, -$\overset{|}{\mathrm{C}}\underline{\mathrm{H}}$OH); mass spectr m/e 194.1309 (M-18) (Calcd. for $C_{12}H_{18}O_2$: 194.1307. al. Calcd. for $C_{12}H_{18}O_2$: C, 67.92; H, 9.48. Foun C, 68.14; H, 9.63.

5-Acetoxy-7 acetoxymethyl-3-methyltricyclo[5.3.0.0^{2,6}]-decan-1-ol 140)

To a s lution of 25 mg (0.082 mmol) of 136 in 1.5 ml of pyric ne, was added 0.15 ml of acetic anhydride. The reactic mixture was stirred at room temperature under an at osphere of nitrogen for 72 h. After cooling to 0°C, it as poured into 20 ml of ice-cold 3N hydrochloric ac and extracted with ether (3 x 120 ml). The extrac were washed successively with saturated aqueous so um bicarbonate (25 ml) and water (25 ml).

Drying, filtration and concentration of the dried extracts gave 38 mg of a solid. Recrystallization from ether yielded 32 mg (92%) of 140: mp 108-109°C; ir (CCl_4) 3600, 3500 (hydroxy) and 1730 cm^{-1} (esters); ^1H nmr (CCl_4) δ 0.97 (d, 3H, J = 6.5 Hz, $>CHC\underline{H}_3$), 2.06 (s, 6H, CH_3COO-), 4.28, 4.46, (both d, 1H each, J = 12 Hz, $-CH_2O-$) and 5.26 (dt, 1H, J = 10, J' = 6 Hz, $-\overset{|}{C}\underline{H}O-$); mass spectrum m/e 236.1425 (M-60) (Calcd. for $C_{14}H_{20}O_3$: 236.1412). Anal. Calcd. for $C_{14}H_{20}O_3$: C, 64.86; H, 8.10. Found: C, 65.10; H, 8.16.

8-Acetoxy-10-methyl-6-methylidenetricyclo[5.3.0]decan-2-one (141)

To a solution of 140 (26 mg, 0.08 ml) in 3 ml of DMSO, was added sodium hydride (6 mg, 0.25 mmol). After stirring at room temperature under an atmosphere of argon for 1 h, the reaction mixture was diluted with 20 ml of ether and poured into 25 ml of water and extracted with ether (3 x 100 ml). The combined ether solution was washed twice with water (20 ml each), dried, filtered, and concentrated to give 25 mg of an oil. Purification of the crude product by column chromatography with ether-benzene (1:20) elution afforded 141 (14 mg, 71%): ir (CCl_4), 3100 (olefin), 1735 (ester), 1710 (ketone), 1645 and 900 cm^{-1} (double bond); ^1H nmr (CCl_4) δ 1.07 (d, 3H, J = 6.5 Hz, $>CHC\underline{H}_3$), 1.98 (s, 3H, CH_3COO-), 4.85, 4.91 (both d, 1H each, J = 1 Hz, $=CH_2$) and 5.29 (dt, 1H, J = 10, J' = 6 Hz, $-\overset{|}{\mathrm{C}}\underline{\mathrm{H}}\mathrm{O}-$); mass spectrum M^+ 236.1409 (Calcd. for $C_{14}H_{20}O_3$: 236.1412).

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